State Coverage Information

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES CII

To view coverage for Xtampza ER,
please click on your state below.

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View payer authorization forms at **CollegiumCoverage.com**

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium® PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Alabama

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Alabama	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
OptumRx	P	Navitus Health Solutions®	PE
State of Alabama Employees	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and Public Education Employee Health Plan.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Alaska

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Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Government Employee Health Association (GEHA)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE and Premera, Inc. health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
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- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

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- **Limit dosages and durations to the minimum required.**
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- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

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ER=extended-release.

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IMPORTANT SAFETY INFORMATION (continued)

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- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Arizona

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and MedImpact health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Arkansas

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Arkansas BCBS	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Elixer PBM	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and AR State Public School EBD health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

California

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CalPERS	P	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and Western Health Advantage health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium® PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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CA

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Colorado

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Government Employee Health Association (GEHA)	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and MedImpact health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Connecticut

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
BCBS of Massachusetts *NEW*	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
Empire NY State Employees Plan	P		
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization requirements at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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CT

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

District of Columbia

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Montgomery County Employees (MD)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium® PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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DC

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Delaware

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Commercial		Commercial & Medicare Part D	
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Bank of America	PE	Humana	PE
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- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

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Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

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- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Florida

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Florida Blue	PE
CVS Caremark	PE	Health First	PE
OptumRx	P	Humana	PE
State of Florida Employees	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Florida
Tallahassee

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Alabama	PE
AT&T	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Florida Blue	PE
CVS Caremark	PE	Humana	PE
OptumRx	P	UnitedHealthcare	PE
State of Florida Employees	P		

Xtampza ER is also covered on TRICARE, Anthem and Capital Health Plan health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Georgia

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Alabama	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
OptumRx	P	Navitus Health Solutions®	PE
State Health Benefit Plan Employees	PE	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Idaho

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
AT&T	P	Humana	PE
BCBS Federal Employee Program (FEP)	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	SelectHealth	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and Regence BCBS health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Illinois

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
CVS Caremark	PE	Cigna and Cigna-HealthSpring†	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	Humana	PE
OptumRx	P	Navitus Health Solutions®	PE
State of Illinois Employees (SERS)	PE	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Indiana

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
General Motors	PE	UnitedHealthcare	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE		
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Life-Threatening Respiratory Depression
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Accidental Ingestion
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Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
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ER=extended-release.

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IMPORTANT SAFETY INFORMATION (continued)

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- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

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- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

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- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Kansas

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
BCBS Federal Employee Program (FEP)	P	BCBS of South Carolina	P
BCBS of Kansas	PE	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Elixer PBM	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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KS

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Kentucky

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
Commonwealth of Kentucky	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and Alcoa Inc. health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

KY

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Louisiana

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Elixer PBM	PE	People's Health	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and LA Office of Group Benefits health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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LA

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Maine

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
BCBS of Massachusetts *NEW*	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
Harvard Pilgrim Health Care	PE		
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

ME

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Maryland

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE
State of Maryland Employees	PE		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Massachusetts

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
BCBS of Massachusetts *NEW*	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
Harvard Pilgrim Health Care	PE		
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium® PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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MA

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Michigan

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- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
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- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Minnesota

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
OptumRx	P	Navitus Health Solutions®	PE
State of Minnesota Employees	PE	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and HealthPartners health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium® PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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MN

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Mississippi

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Alabama	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Huntington Ingalls Industries Employees	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem and BCBS of Mississippi health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

MS

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Missouri

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Elixer PBM	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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MO

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Nebraska

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Nebraska	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Elixer PBM	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Nevada

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

New Hampshire

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
BCBS of Massachusetts *NEW*	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
Harvard Pilgrim Health Care	PE		
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

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- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

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ER=extended-release.

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IMPORTANT SAFETY INFORMATION (continued)

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- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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NJ

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

New York

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Independence Blue Cross	PE
Empire NY State Employees Plan	P	Navitus Health Solutions®	PE
Excellus BCBS	P	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

North Carolina

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of North Carolina	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
NC Teachers and State Employees	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

North Dakota

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Elixer PBM	PE	Navitus Health Solutions®	PE
ND Public Employees Retirement System	PE	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and MedImpact health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Ohio

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Ohio Bureau of Workers Comp	PE	UnitedHealthcare	PE
Ohio State Employer Benefit Plan	P		
OptumRx	P		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Oklahoma

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and MedImpact health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Oregon

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Elixer PBM	PE	Providence Health Systems	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and Regence BCBS health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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OR

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Pennsylvania

Compared to OxyContin, Xtampza ER nationally has:

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- ✓ More lives covered[2]
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Commercial		Commercial & Medicare Part D	
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BCBS Federal Employee Program (FEP)	P	Independence Blue Cross	PE
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OptumRx	P	UnitedHealthcare	PE
Pennsylvania Employee Benefit Trust Fund (PEBTF)	PE	UPMC	PE

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P= Preferred—the lowest branded co-pay for the majority of covered lives
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- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

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Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

PA

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Rhode Island

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
BCBS of Massachusetts *NEW*	PE	Navitus Health Solutions®	PE
CVS Caremark	PE	UnitedHealthcare	PE
Harvard Pilgrim Health Care	PE		
State of Rhode Island Employees	PE		

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

South Carolina

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of North Carolina	PE
BCBS Federal Employee Program (FEP)	P	BCBS of South Carolina	P
CVS Caremark	PE	Cigna and Cigna-HealthSpring†	PE
Elixer PBM	PE	Humana	PE
OptumRx	P	Navitus Health Solutions®	PE
		UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE and Anthem health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit **XtampzaER.com**. To contact a Collegium sales representative, call **1-888-884-2655.**

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

South Dakota

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Mail Handlers Benefit Plan	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and Avera Health health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to
- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.
- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Tennessee

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and State of Tennessee Employees health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Texas

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
HCSC (BCBS TX, IL, OK, NM, MT)	PE	UnitedHealthcare	PE
OptumRx	P		

Xtampza ER is also covered on TRICARE, Anthem, and HealthSelect of Texas ERS health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Utah

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Mail Handlers Benefit Plan	PE	SelectHealth	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem and Regence BCBS health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Vermont

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- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
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- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

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ER=extended-release.

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IMPORTANT SAFETY INFORMATION (continued)

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- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Virginia

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of North Carolina	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Elixer PBM	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and Optima Health health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Washington

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Elixer PBM	PE	Providence Health Systems	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and Regence BCBS health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium® PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

WA

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

West Virginia

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	Cigna and Cigna-HealthSpring†	PE
BCBS Federal Employee Program (FEP)	P	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
Ohio Bureau of Workers Comp	PE	UnitedHealthcare	PE
OptumRx	P	UPMC	PE

Xtampza ER is also covered on TRICARE, Anthem, and MedImpact health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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WV

Collegium PHARMACEUTICAL

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Wisconsin

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
CVS Caremark	PE	Humana	PE
Dean Health	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem and WI University Health Care health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Collegium PHARMACEUTICAL

IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

It's time to transition your OxyContin® patients to Xtampza® ER

Wyoming

Compared to OxyContin, Xtampza ER nationally has:

- ✓ Lower average co-pays[1]
- ✓ More lives covered[2]
- ✓ Higher approval rates[1]

Xtampza ER is the preferred ER oxycodone

for most national and regional health plans and pharmacy benefit managers

Commercial		Commercial & Medicare Part D	
Aetna	PE	BCBS of Minnesota	PE
BCBS Federal Employee Program (FEP)	P	Cigna and Cigna-HealthSpring†	PE
BCBS of Wyoming	PE	Humana	PE
CVS Caremark	PE	Navitus Health Solutions®	PE
OptumRx	P	UnitedHealthcare	PE

Xtampza ER is also covered on TRICARE, Anthem, and State of Wyoming Employees health plans.

P= Preferred—the lowest branded co-pay for the majority of covered lives
E= Exclusive—the only branded ER oxycodone on formulary for the majority of covered lives
Please see reverse side for specific plan exceptions. Stated coverage is not a guarantee and is subject to change without notice.

View your state's coverage and authorization forms at **CollegiumCoverage.com**

To learn more, visit XtampzaER.com. To contact a Collegium sales representative, call 1-888-884-2655.

INDICATIONS AND USAGE

Xtampza® ER (oxycodone) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse and Misuse
Xtampza ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

Accidental Ingestion
Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Xtampza ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

CONTRAINDICATIONS:

- Xtampza ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg, anaphylaxis) to oxycodone.

WARNINGS AND PRECAUTIONS:

Addiction, Abuse, and Misuse
Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present.

ER=extended-release.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at XtampzaER.com/PI.

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IMPORTANT SAFETY INFORMATION (continued)

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved.
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients With Chronic Pulmonary Disease: Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg.

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

Severe Hypotension

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

Risks of Use in Patients With Gastrointestinal Conditions

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

Risk of Use in Patients With Seizure Disorders

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

Withdrawal

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

Risks of Driving and Operating Machinery

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

Laboratory Monitoring

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

ADMINISTRATION WITH FOOD:

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

ADVERSE REACTIONS:

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

References: 1. IQVIA FIA December 2020. **2.** Managed Markets Insight & Technology, LLC (MMIT) data as of February 2021, Data on File.

†Excluding Leon Medicare Advantage-Prescription Drug (MA-PD)

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