INDICATIONS AND USAGE

XTAMPZA® ER (oxycodone) is indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, 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 ABOUT XTAMPZA ER

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF XTAMPZA ER

Addiction, Abuse, and Misuse
Because the use of 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 and reassess all patients regularly for the development of these behaviors and conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of XTAMPZA ER, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of XTAMPZA ER are essential.

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

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)
If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription.

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. Regularly evaluate patients receiving XTAMPZA ER and any CYP3A4 inhibitor or inducer.

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. Because 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.
- Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed XTAMPZA ER. Addiction can occur at recommended dosages and if the drug is misused or abused.
- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing XTAMPZA ER, and reassess all patients receiving XTAMPZA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as XTAMPZA ER but use in such patients necessitates intensive counseling about the risks and proper use of XTAMPZA ER along with frequent evaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose.
- Abuse or misuse of XTAMPZA ER by snorting or by injecting the dissolved product can result in overdose and death.
- Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing XTAMPZA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and the proper disposal of unused drug. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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.

<u>Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:</u>

- 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.

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 and/or other CNS depressants, including alcohol (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). 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 the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressants than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation).
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.
- Advise both patients and caregivers about the risks of respiratory depression and sedation when XTAMPZA ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

Neonatal Opioid Withdrawal Syndrome (NOWS)
- Use of XTAMPZA ER for an extended period of time 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 NOWS and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of NOWS, and ensure that appropriate treatment will be available.

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 the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. 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 that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

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

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, evaluate 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.

Opioid-Induced Hyperalgesia and Allodynia

- Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.
- Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety).

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.
- Regularly evaluate 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 non-specific 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). Regularly evaluate 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. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures 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. Regularly evaluate 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 then administering directly into the mouth, or through a gastrostomy or nasogastric 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.

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