HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XTAMPZA® ER safely and effectively. See full prescribing information for XTAMPZA ER.

XTAMPZA ER (oxycodone) extended-release capsules, for oral use, CII
Initial U.S. Approval: 1950

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

See full prescribing information for complete boxed warning.

- **XTAMPZA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and reassess regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of XTAMPZA ER are essential. (5.2)**
- **Accidental ingestion of XTAMPZA ER, especially by children, can result in fatal overdose of oxycodone. (5.2)**
- **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 for use in patients for whom alternative treatment options are inadequate. (5.3, 7)**
- **Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.4)**
- **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. (5.5)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from XTAMPZA ER. (5.6, 12.3)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning ---------- 12/2025
Indications and Usage (1) ---------- 12/2025
Dosage and Administration (2.1, 2.3, 2.5) ---------- 12/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.14) ---------- 12/2025

---------- INDICATIONS AND USAGE ----------

XTAMPZA ER is an opioid agonist indicated for the management of severe and persistent pain that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids.(1)

Limitations of Use (1)

- Because of the risks of addiction, abuse, misuse, overdose, and death,which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including XTAMPZA ER, for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1, 5.1)
- XTAMPZA ER is not indicated as an as-needed (prn) analgesic. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- XTAMPZA ER should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks. (2.1)
- XTAMPZA ER at a total daily dose greater than 72 mg (equivalent to 80 mg oxycodone hydrochloride [HCl]) or a single dose greater than 36 mg (equivalent to 40 mg oxycodone HCl) is only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone HCl per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dose for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of XTAMPZA ER for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2, 5)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse (2.1, 5.1).
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with XTAMPZA ER. Consider this risk when selecting an initial dose and when making dose adjustments (2.1, 5.2)
- Discuss opioid overdose reversal agents and options for acquiring them with the patient and/or caregiver, both when initiating and renewing treatment with XTAMPZA ER, especially if the patient has additional risk factors for overdose, or close contacts at risk for exposure and overdose. (2.2, 5.1, 5.2, 5.3)
- XTAMPZA ER is administered, twice daily, every 12 hours, and **must be taken with food**. Instruct patients to take XTAMPZA ER capsules with approximately the same amount of food for every dose to ensure consistent plasma levels are achieved. (2.1, 2.3)
- For patients who are not opioid tolerant, initiate with 9 mg (equivalent to 10 mg oxycodone HCl per day). (2.3)
- The daily dose of XTAMPZA ER must be limited to a maximum of 288 mg per day (equivalent to 320 mg oxycodone HCl per day). (2.1)
- Hepatic impairment: Initiate therapy at 1/3 to 1/2 the usual dosage and titrate carefully. Regularly evaluate. Use alternate analgesia for patients requiring less than 9 mg. (2.4, 8.6)
- Periodically reassess patients receiving XTAMPZA ER to evaluate the continued need for opioid analgesics to maintain pain control, for the signs or symptoms of adverse reactions, and for the development of addiction, abuse, or misuse. (2.5)
- Do not rapidly reduce or abruptly discontinue XTAMPZA ER in a physically-dependent patient because rapid reduction or abrupt discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.6, 5.14)
- Instruct patients to take XTAMPZA ER capsules with food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, XTAMPZA ER can also be taken by sprinkling the capsule contents on soft foods or into a cup and then administering directly into the mouth, or through a gastrostomy or nasogastric feeding tube. (2.7)

---------- DOSAGE FORMS AND STRENGTHS ----------

Extended-release capsules:

- 9 mg (equivalent to 10 mg oxycodone HCl)
- 13.5 mg (equivalent to 15 mg oxycodone HCl)
- 18 mg (equivalent to 20 mg oxycodone HCl)
- 27 mg (equivalent to 30 mg oxycodone HCl)
- 36 mg (equivalent to 40 mg oxycodone HCl). (3)

---------- CONTRAINDICATIONS ----------

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

---------- WARNINGS AND PRECAUTIONS ----------

- 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. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.7)
- Risk of life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients: Regularly evaluate. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe hypotension: Regularly evaluate. Avoid use of XTAMPZA ER in patients with circulatory shock. (5.10)
- Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness: Monitor for sedation and respiratory depression. Avoid use of XTAMPZA ER in patients with impaired consciousness or coma. (5.11)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (>5%) were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Collegium Pharmaceutical, Inc. at 1-855-331-5615 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

- CNS depressants: Concomitant use may cause profound sedation, respiratory depression, coma, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects and frequently evaluate. (5.3, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue XTAMPZA ER if serotonin syndrome is suspected. (7)
- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with XTAMPZA ER because they may reduce analgesic effect of XTAMPZA ER or precipitate withdrawal symptoms. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of oxycodone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of XTAMPZA ER, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

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 *[see Warnings and Precautions (5.5)]*.

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 *[see Warnings and Precautions (5.6), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

1 INDICATIONS AND USAGE

XTAMPZA ER is indicated for the management of severe and persistent pain that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids.

Limitations of Use

- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy *[see Warnings and Precautions (5.1)]*, reserve opioid analgesics, including XTAMPZA ER, for use in patients for whom alternative treatment options 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- XTAMPZA ER should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks.
- XTAMPZA ER single doses greater than 36 mg (equivalent to 40 mg oxycodone hydrochloride [HCl]) or a total daily dose greater than 72 mg (equivalent to 80 mg oxycodone HCl) are to be administered only to patients in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid-tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone HCl per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of XTAMPZA ER for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with XTAMPZA ER. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5.2)]*.
- XTAMPZA ER is administered, twice daily, every 12 hours, and **must be taken with food.** Instruct patients to take XTAMPZA ER capsules with approximately the same amount of food for every dose in order to ensure consistent plasma levels are achieved *[see Clinical Pharmacology (12.3)]*.
- Patients who are unable to swallow XTAMPZA ER should be instructed to sprinkle the capsule contents on soft foods or into a cup and then administer directly into the mouth and immediately swallow. XTAMPZA ER may also be administered through a gastrostomy or nasogastric feeding tube *[see Dosage and Administration (2.7)]*.
- The maximum daily dose of XTAMPZA ER is 288 mg per day (eight 36 mg capsules, equivalent to 320 mg oxycodone HCl per day) as the safety of the excipients in XTAMPZA ER for doses over 288 mg/day has not been established.

2.2 Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) [*see Warnings and Precautions (5.2)]*.

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

2.3 Initial Dosage

It is safer to underestimate a patient's 24-hour oral oxycodone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone dosage and manage adverse reactions due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. Frequently reevaluate patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to XTAMPZA ER.

Use of XTAMPZA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is XTAMPZA ER 9 mg orally every 12 hours with food. Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.2)]*.

Conversion from other Oral Oxycodone Formulations to XTAMPZA ER

XTAMPZA ER is formulated with oxycodone base. The following table describes the equivalent amount of oxycodone HCl present in other oxycodone products.

Table 1. Equivalence table for dosage strengths of oxycodone hydrochloride salt and oxycodone base (XTAMPZA ER)

Oxycodone Hydrochloride	Oxycodone base (XTAMPZA ER)
10 mg	9 mg
15 mg	13.5 mg
20 mg	18 mg
30 mg	27 mg
40 mg	36 mg

Patients receiving other oral oxycodone formulations may be converted to XTAMPZA ER, using the same total daily dose of oxycodone, by administering one-half of the patient's total daily oral oxycodone dose as XTAMPZA ER every 12 hours with food. Because XTAMPZA ER is not bioequivalent to other oxycodone extended-release products (refer to Table 1), monitor patients for possible dosage adjustment.

Conversion from Methadone to XTAMPZA ER

Frequent evaluation is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Fentanyl Transdermal System to XTAMPZA ER

Eighteen hours following the removal of the fentanyl transdermal system, XTAMPZA ER treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 9 mg (equivalent to 10 mg oxycodone HCl) every 12 hours of XTAMPZA ER, should be initially substituted for each 25 mcg/hr fentanyl transdermal system. Follow the patient closely during conversion from fentanyl transdermal system to XTAMPZA ER, as there is limited documented experience with this conversion.

Conversion from Other Opioid Analgesics to XTAMPZA ER

When XTAMPZA ER therapy is initiated, discontinue all other opioid analgesics other than those used on an as needed basis for breakthrough pain when appropriate.

There are no established conversion ratios for conversion from other opioids to XTAMPZA ER defined by clinical trials. Initiate dosing using XTAMPZA ER 9 mg orally every 12 hours with food.

2.4 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration. Regularly evaluate for adverse events such as respiratory depression. Use of alternate analgesics is recommended for patients who require an XTAMPZA ER dose of less than 9 mg *[see Use in Specific Populations (8.5), Clinical Pharmacology (12.3)]*.

2.5 Titration and Maintenance of Therapy

Individually titrate XTAMPZA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving XTAMPZA ER to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as to reassess for the development of addiction, abuse, and misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During use of opioid therapy for an extended period of time, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of XTAMPZA ER or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the XTAMPZA ER dose. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Because steady-state plasma concentrations are approximated in 1 to 2 days, XTAMPZA ER dosage may be adjusted every 1 to 2 days. If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

2.6 Safe Reduction or Discontinuation of XTAMPZA ER

Do not rapidly reduce or abruptly discontinue XTAMPZA ER in patients who may be physically dependent on opioids. Rapid reduction or abrupt discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid reduction or abrupt discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking XTAMPZA ER, there are a variety of factors that should be considered, including the total daily dose of opioid (including XTAMPZA ER) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance

use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on XTAMPZA ER who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time, and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

2.7 Administration of XTAMPZA ER

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 *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

For patients who have difficulty swallowing, XTAMPZA ER can also be taken by sprinkling the capsule contents on soft foods or sprinkling the contents into a cup and then administering directly into the mouth or through a gastrostomy or nasogastric feeding tube. Patients who are unable to swallow a capsule should be instructed to:

1. Open the capsule.
2. Sprinkle the capsule contents (microspheres) onto a small amount of soft food (e.g., applesauce, pudding, yogurt, ice cream, or jam) or into a cup and then administer directly into the mouth and swallow immediately.
3. Rinse the mouth to ensure all capsule contents (microspheres) have been swallowed.
4. Discard the XTAMPZA ER capsule shells after the contents have been sprinkled on soft food or into a cup and then administered directly into the mouth.

The contents of the XTAMPZA ER capsules (microspheres) may be administered through a nasogastric tube or gastrostomy tube. When administering XTAMPZA ER through a nasogastric or gastrostomy tube:

1. Flush the tube with water.
2. Open an XTAMPZA ER capsule and carefully pour the microspheres directly into the tube. Do not pre-mix the capsule contents with the liquid that you will be using to flush them through the tube.
3. Draw up 15 mL of water into a syringe, insert the syringe into the tube, and flush the microspheres through the tube.
4. Repeat the flushing two more times, each with 10 mL of water, to ensure no microspheres remain in the tube.

Alternatively, milk or liquid nutritional supplement may be used as vehicles for flush and administration through feeding tubes.

3 DOSAGE FORMS AND STRENGTHS

XTAMPZA ER capsules contain yellow to light brown microspheres, and each available strength has an outer opaque capsule with colors as identified below.

Strength	Capsule Description
9 mg (equivalent to 10 mg oxycodone HCl)	Size 3, ivory cap printed with “XTAMPZA ER” and white body printed with “9 mg”
13.5 mg (equivalent to 15 mg oxycodone HCl)	Size 2, Swedish orange cap printed with “XTAMPZA ER” and white body printed with “13.5 mg”
18 mg (equivalent to 20 mg oxycodone HCl)	Size 1, rich yellow cap printed with “XTAMPZA ER” and white body printed with “18 mg”
27 mg (equivalent to 30 mg oxycodone HCl)	Size 0, light gray cap printed with “XTAMPZA ER” and white body printed with “27 mg”
36 mg (equivalent to 40 mg oxycodone HCl)	Size 00, flesh color cap printed with “XTAMPZA ER” and white body printed with “36 mg”

4 CONTRAINDICATIONS

XTAMPZA ER is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity (e.g., anaphylaxis) to oxycodone.

5 WARNINGS AND PRECAUTIONS

5.1 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 *[see Drug Abuse and Dependence (9)]*.

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. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6.2)]*.

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 recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Abuse or misuse of XTAMPZA ER by snorting or by injecting the dissolved product can result in overdose and death *[see Overdosage (10)]*.

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.

5.2 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 overdose reversal agents, depending on the patient’s clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of XTAMPZA ER, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of XTAMPZA ER are essential *[see Dosage and Administration (2)]*. Overestimating the XTAMPZA ER dose

when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of XTAMPZA ER, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

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 *[see Dosage and Administration (2.6)]*.

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.2)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent. outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

5.3 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 (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, gabapentinoids [gabapentin or pregabalin], and 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 *[see Drug Interactions (7)]*.

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 recommending or prescribing an opioid overdose reversal agent for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

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 *[see Drug Interactions (7)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

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 neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

5.5 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 using 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 opioid analgesic REMS and for 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.

5.6 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 (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.2)]*, 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 at frequent intervals and consider dosage reduction of XTAMPZA ER until stable drug effects are achieved *[see Drug Interactions (7)]*.

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, evaluate patients at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.7 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 *[see Dependence (9.3)]*. 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) *[see Dosage and Administration (2.6), Warnings and Precautions (5.14)]*.

5.8 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 *[see Warnings and Precautions (5.2)]*.

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, particularly when initiating and titrating XTAMPZA ER and when XTAMPZA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.3)]*. 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.

5.9 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.

5.10 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 (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. 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.

5.11 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 (e.g., 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.

5.12 Risks of Gastrointestinal Complications

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 with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate *[see Clinical Pharmacology (12.2)]*.

5.13 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.

5.14 Withdrawal

Do not rapidly reduce or 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 *[see Dosage and Administration (2.6), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., 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 *[see Dosage and Administration (2.6), Drug Interactions (7)]*.

5.15 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.

5.16 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.7)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.9)]*
- Severe Hypotension *[see Warnings and Precautions (5.10)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of XTAMPZA ER was evaluated in a Phase 3, randomized-withdrawal, double-blind clinical trial involving 740 patients with moderate-to-severe chronic lower back pain. In the double-blind maintenance phase, 389 patients were randomized and 193 patients were assigned to the XTAMPZA ER treatment group.

The most common AEs (>5%) reported by patients in the Phase 3 clinical trial during the titration phase were: nausea (16.6%), headache (13.9%), constipation (13.0%), somnolence (8.8%), pruritus (7.4%), vomiting (6.4%), and dizziness (5.7%).

The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing XTAMPZA ER with placebo are shown in Table 2 below:

Table 2: Common Adverse Reactions (>5%)

	Titration	Maintenance	
Adverse Reaction	XTAMPZA ER (n = 740) (%)	XTAMPZA ER (n = 193) (%)	Placebo (n = 196) (%)
Nausea	16.6	10.9	4.6
Headache	13.9	6.2	11.7
Constipation	13.0	5.2	0.5
Somnolence	8.8	<1	<1
Pruritus	7.4	2.6	1.5
Vomiting	6.4	4.1	1.5
Dizziness	5.7	1.6	0

In the Phase 3 clinical trial, the following adverse reactions were reported in patients treated with XTAMPZA ER with incidences of 1% to 5%:

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal pain, upper abdominal pain, diarrhea, gastroesophageal reflux disease

General disorders and administration site conditions: chills, drug withdrawal syndrome, fatigue, irritability, edema, pyrexia

Injury, poisoning and procedural complications: excoriation

Metabolism and nutrition disorders: decreased appetite, hyperglycemia

Musculoskeletal and connective tissue disorders: arthralgia, back pain, musculoskeletal pain, myalgia

Nervous system disorders: migraine, tremor

Psychiatric disorders: anxiety, insomnia, withdrawal syndrome

Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain

Skin and subcutaneous tissue disorders: hyperhidrosis, rash

Vascular disorders: hot flush, hypertension

In the Phase 3 clinical trial, the following treatment-related adverse reactions were

reported in patients treated with XTAMPZA ER with incidences of **less than 1% of patients.**

Investigations: increased gamma-glutamyl transferase, increased heart rate

Nervous system disorders: lethargy, memory impairment, poor-quality sleep

Psychiatric disorders: abnormal dreams, euphoric mood, restlessness

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: night sweats

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in XTAMPZA ER.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)]*.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.7)]*.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.12)]*.

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with XTAMPZA ER.

TABLE 3: CLINICALLY SIGNIFICANT DRUG INTERACTIONS WITH XTAMPZA ER

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of XTAMPZA ER and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of XTAMPZA ER and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of XTAMPZA ER is achieved *[see Warnings and Precautions (5.6)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of XTAMPZA ER until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the XTAMPZA ER dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of XTAMPZA ER and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)],* resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.6)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)],* which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the XTAMPZA ER dosage until stable drug effects are achieved *[see Dosage and Administration (2.5)]*. Evaluate patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider XTAMPZA ER dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacological effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death *[see Warnings and Precautions (5.3)]*.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. 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 recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue XTAMPZA ER if serotonin syndrome is suspected.

Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*.
Intervention:	The use of XTAMPZA ER is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of XTAMPZA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of XTAMPZA ER and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
Examples	Cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when XTAMPZA ER is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no available data with XTAMPZA ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when oxycodone hydrochloride was orally administered to rats and rabbits, during the period of organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 160 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration of use, and severity of neonatal opioid withdrawal syndrome may vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [*see Warnings and Precautions (5.4)]*.

Labor or delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene, must be available for reversal of opioid induced respiratory depression in the neonate. XTAMPZA ER is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including XTAMPZA ER, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 1.3 and 40 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by dams given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered. In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3-times an adult human oral dose of 60 mg/day on a mg/m^2 basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended-release oxycodone, including XTAMPZA ER, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with XTAMPZA ER.

Clinical Considerations

Monitor infants exposed to XTAMPZA ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of XTAMPZA ER in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects entered into the titration phase of

the Phase 3 study for XTAMPZA ER (740), 88 (12%) were age 65 and older. In this clinical trial with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received XTAMPZA ER. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. Use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease, and use of other drug therapy.

Respiratory depression is the chief risk in elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of XTAMPZA ER slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)]*.

8.6 Hepatic Impairment

A study in patients with hepatic impairment demonstrated greater plasma oxycodone concentrations than those seen at equivalent doses in persons with normal hepatic function. A similar effect on plasma oxycodone concentrations can be expected for patients with hepatic impairment taking XTAMPZA ER. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration. Use of alternative analgesics is recommended for patients who require a dose of XTAMPZA ER less than 9 mg *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation. Use of alternative analgesics is recommended for patients who require a dose of XTAMPZA ER less than 9 mg *[see Clinical Pharmacology (12.3)]*.

8.8 Sex Differences

In pharmacokinetic studies with XTAMPZA ER, healthy female subjects demonstrate up to 20% higher oxycodone plasma exposures than males, even after considering differences in body weight or BMI. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages. In the Phase 3 clinical trial there was a greater frequency of typical opioid adverse events for females than males; there was no male/female difference detected for efficacy.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XTAMPZA ER contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

XTAMPZA ER contains oxycodone, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of XTAMPZA ER increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of XTAMPZA ER with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of XTAMPZA ER abuse include those with a history of prolonged use of any opioid, including products containing buprenorphine, those with a history of drug or alcohol abuse, or those who use XTAMPZA ER in combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

XTAMPZA ER, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of XTAMPZA ER

Abuse of XTAMPZA ER poses a risk of overdose and death. The risk is increased with concurrent use of XTAMPZA ER with alcohol and/or other CNS depressants *[see Warnings and Precautions (5.1, 5.3), Drug Interactions (7)]*.

XTAMPZA ER is approved for oral use only.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Abuse Deterrence Studies

XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the formulation more difficult to manipulate for misuse and abuse.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the success of different methods of defeating the extended-release formulation.

Results support that, relative to immediate-release oxycodone tablets, XTAMPZA ER is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents.

XTAMPZA ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle.

Pharmacokinetic Studies

The pharmacokinetic profile of manipulated XTAMPZA ER capsule contents (36 mg; [equivalent to 40 mg oxycodone HCl]) was characterized following oral (three studies) and intranasal (two studies) administration. The studies were conducted in a randomized, cross-over design. In studies assessing manipulation by crushing, the most effective crushing method identified in previous *in vitro* studies was applied to the product(s).

Oral Pharmacokinetic Studies, Manipulated and Intact XTAMPZA ER

The effect of two types of product manipulation (crushing and chewing) on XTAMPZA ER pharmacokinetics was measured in three studies.

In one oral pharmacokinetic study, XTAMPZA ER capsule contents were crushed or chewed prior to oral administration in healthy, naltrexone-blocked volunteers. The two comparators in this study were intact XTAMPZA ER capsules and an immediate-release solution of oxycodone at an equivalent dose.

In two oral pharmacokinetic studies, XTAMPZA ER capsule contents were crushed prior to oral administration in healthy, naltrexone-blocked volunteers. The comparators in these studies included intact XTAMPZA ER capsules, intact and crushed reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets at an equivalent dose, and crushed immediate-release oxycodone tablets at an equivalent dose.

The data displayed in Table 4 illustrate the findings from the oral pharmacokinetic studies (data were similar for the two oral pharmacokinetic studies comparing XTAMPZA ER to OXYCONTIN). Collectively, the data demonstrated that crushing or chewing XTAMPZA ER prior to administration did not increase the maximum observed plasma concentration (C_{max}) or total exposure ($AUC_{0\text{-}INF}$) relative to dosing the intact product under fed conditions. Relative to immediate-release oxycodone and crushed reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets, the C_{max} for all XTAMPZA ER treatments was lower and the T_{max} longer, consistent with an extended-release profile.

Table 4: Oxycodone Pharmacokinetic Parameters, Administration of Manipulated and Intact Dosage Forms (36 mg of XTAMPZA ER or equivalent)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-INF} (hr•ng/mL)
Treatment	**Oral Pharmacokinetic Study 1**		
Intact XTAMPZA ER Capsules (fed)	62.3 (13.0)	4.0 (1.5-6)	561 (124)
Crushed XTAMPZA ER Capsule Contents (fed)	57.6 (12.6)	4.5 (2.5-6)	553 (134)
Chewed XTAMPZA ER Capsule Contents (fed)	55.6 (10.9)	4.5 (2.5-8)	559 (113)
Immediate-Release Oxycodone Solution (fasted)	115 (27.3)	0.75 (0.5-2)	489 (80.2)
	Oral Pharmacokinetic Study 2		
Intact XTAMPZA ER Capsules (fed)	67.5 (17.6)	3.5 (1.25-6.0)	581 (138)
Crushed XTAMPZA ER Capsule Contents (fed)	62.9 (12.6)	4.0 (2.0-7.0)	597 (149)
Intact reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets (fed)	64.9 (13.8)	5.0 (2.0-10.0)	611 (145)
Crushed reformulated OXYCONTIN (oxycodone hydrochloride) extended-release tablets (fed)	78.4 (12.9)	1.75 (0.5-5.0)	587 (132)
Crushed Immediate-Release Oxycodone Tablets (fed)	79.4 (17.1)	1.75 (0.5-4.0)	561 (146)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Studies

The pharmacokinetic profile following intranasal administration of crushed XTAMPZA ER capsule contents was characterized in two clinical studies.

In Nasal Pharmacokinetic Study 1, XTAMPZA ER capsule contents (36 mg) were crushed and intranasally administered by non-dependent, naltrexone-blocked subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and oxycodone HCl powder (intranasal) at an equivalent dose.

In Nasal Pharmacokinetic Study 2, XTAMPZA ER capsule contents (36 mg) were crushed and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and crushed oxycodone immediate-release tablets (intranasal) at an equivalent dose.

The results of Nasal Pharmacokinetic Studies 1 and 2 are comparable and both studies demonstrated that intranasal administration of crushed XTAMPZA ER capsule contents did not result in higher peak plasma concentration (C_{max}) or shorter time to peak concentration (T_{max}) than taking XTAMPZA ER orally. The data from Nasal Pharmacokinetic Study 2 are displayed in Table 5 to represent these findings.

Table 5: Oxycodone Pharmacokinetic Parameters, Nasal Pharmacokinetic Study 2

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-INF} (hr•ng/mL)
Intact XTAMPZA ER Capsules (oral)	41.0 (10.0)	5.1 (1.6-8.1)	477 (89.6)
Crushed XTAMPZA ER Capsule Contents (nasal)	29.8 (6.6)	5.1 (1.6-12.1)	459 (106)
Crushed Immediate-Release Tablets (nasal)	60.9 (11.9)	2.6 (0.3-6.1)	577 (124)

Values shown for C_{max} and AUC_{0-INF} are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Studies

Oral Abuse Potential Studies:

The oral abuse potential of chewed XTAMPZA ER was evaluated in two studies.

In a randomized, double-blind, active- and placebo-controlled, single-dose, six-way crossover pharmacodynamic study, 52 non-dependent recreational opioid users received orally-administered active and placebo treatment. The six treatment arms were intact XTAMPZA ER (36 mg, fed and fasted); chewed XTAMPZA ER (36 mg, fed and fasted); crushed immediate-release (IR) oxycodone HCl in solution (40 mg, fasted, equivalent to 36 mg of XTAMPZA ER), and placebo. Data for chewed and intact XTAMPZA ER and crushed IR oxycodone in the fasted state are described below.

Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 50 represents a neutral response, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar 100-point VAS where 50 represents a neutral response, 0 represents the strongest negative response (e.g., 'definitely would not take drug again'), and 100 represents the strongest positive response (e.g., 'definitely would take drug again').

Fifty-two subjects completed the study, and the results are summarized in Table 6. The oral administration of chewed and intact XTAMPZA ER in the fasted state was associated with statistically lower mean Drug Liking and Take Drug Again VAS scores compared with crushed immediate-release oxycodone. In addition, the Drug Liking and Take Drug Again scores were similar for XTAMPZA ER taken in the intact and chewed states.

Table 6: Summary of Maximum Drug Liking and Take Drug Again (Emax) Following Oral Administration

		XTAMPZA ER Intact (Fasted)	XTAMPZA ER Chewed (Fasted)	Crushed IR Oxycodone (Fasted)	Placebo
Drug Liking* (E_{max})	Mean (SD)	73.9 (15.10)	73.3 (14.93)	86.40 (12.01)	55.8 (9.94)
	Median (Range)	73.5 (50-100)	73.5 (50-100)	88.5 (52-100)	50.0 (50-86)
Take Drug Again (E_{max})*	Mean (SD)	77.98 (21.07)	77.85 (18.30)	87.69 (12.90)	50.79 (21.41)
	Median (Range)	80.5 (1-100)	81.5 (50-100)	90.5 (50-100)	50.0 (0-100)

* Bipolar scale (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

E_{max} = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SD=Standard Deviation.

A prior, similarly-designed study was also conducted to evaluate the oral abuse potential of chewed XTAMPZA ER. Although the oral administration of chewed and intact XTAMPZA ER in the fasted state was associated with statistically lower mean Drug Liking scores compared with crushed immediate-release oxycodone, the results for Take Drug Again showed small differences that were not statistically significant.

Nasal Abuse Potential Study:

In a randomized, double-blind, active- and placebo-controlled, single-dose, four-way crossover pharmacodynamic study, 39 recreational opioid users with a history of intranasal drug abuse received nasally administered active and placebo drug treatment. The four treatment arms were crushed XTAMPZA ER 36 mg dosed intranasally; intact XTAMPZA ER 36 mg dosed orally; crushed immediate-release oxycodone HCl 40 mg (equivalent to 36 mg of XTAMPZA ER) dosed intranasally; and placebo. Data for intranasal XTAMPZA ER and crushed immediate-release oxycodone are described below.

Thirty-six subjects completed the study. Intranasal administration of crushed XTAMPZA ER was associated with statistically lower mean Drug Liking and Take Drug Again scores compared with crushed immediate-release oxycodone (summarized in Table7).

Table 7: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Intranasal Administration

		XTAMPZA ER Intranasal	Crushed IR Oxycodone Intranasal	Placebo
Drug Liking* (E_{max})	Mean (SD)	61.81 (15.64)	82.72 (10.95)	54.5 (11.77)
	Median (Range)	59.5 (16-94)	84 (60-100)	51 (28-93)
Take Drug Again* (E_{max})	Mean (SD)	47.67 (27.84)	71.36 (23.49)	45.92 (17.50)
	Median (Range)	50 (0-100)	78.5 (18-100)	50 (0-97)

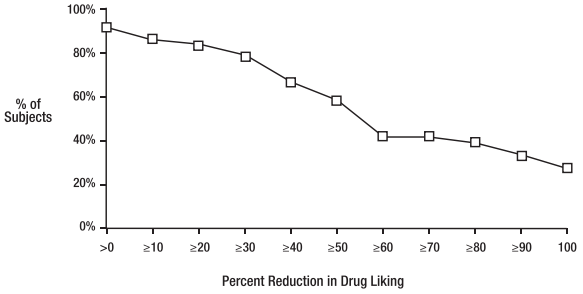
* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SD=Standard Deviation.

Figure 1 demonstrates a comparison of Drug Liking for intranasal administration of crushed XTAMPZA ER compared to crushed immediate-release oxycodone in subjects who received both treatments (N=36). The Y axis represents the percent of subjects attaining a percent reduction in drug liking for XTAMPZA ER vs. immediate-release oxycodone greater than or equal to the value on the X-axis. Approximately 92% (n = 33) of subjects had some reduction in drug liking with XTAMPZA ER relative to crushed immediate-release oxycodone HCl. Approximately 78% (n = 28) of subjects had a reduction of at least 30% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl, and approximately 58% (n = 21) of subjects had

a reduction of at least 50% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Crushed XTAMPZA ER vs. Crushed Immediate-release Oxycodone, N=36 Following Intranasal Administration



Summary

The *in vitro* data demonstrate that XTAMPZA ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from the *in vitro* data, also indicate that XTAMPZA ER has physicochemical properties that are expected to reduce abuse via the oral and intranasal routes. The data from the oral pharmacokinetic studies of crushed or chewed XTAMPZA ER demonstrated a lack of dose dumping with no increase in oxycodone levels compared to intact XTAMPZA ER.

However, abuse of XTAMPZA ER by injection and by the oral and nasal routes of administration is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of XTAMPZA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

XTAMPZA ER contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. XTAMPZA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.3)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Do not rapidly reduce or abruptly discontinue XTAMPZA ER in a patient physically dependent on opioids. Rapid tapering of XTAMPZA ER in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing XTAMPZA ER, gradually taper the dosage using a patient-specific plan that considers the following: the dose of XTAMPZA ER the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.6), Warnings and Precautions (5.14)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

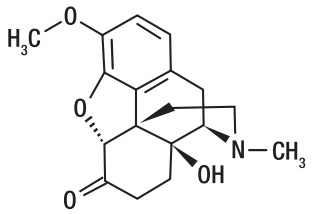
For clinically significant respiratory or circulatory depression secondary to oxycodone overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

Because the duration of reversal would be expected to be less than the duration of action of oxycodone in XTAMPZA ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. XTAMPZA ER will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid overdose reversal agent is suboptimal or only brief in nature, administer additional reversal agent as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the usual dosage of the opioid overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the reversal agent should be begun with care and by titration with smaller than usual doses of the reversal agent.

11 DESCRIPTION

XTAMPZA ER (oxycodone) extended-release capsules are an opioid agonist for oral use. The capsules contain microspheres formulated with oxycodone base and are supplied in strengths of 9 mg (equivalent to 10 mg oxycodone HCl), 13.5 mg (equivalent to 15 mg oxycodone HCl), 18 mg (equivalent to 20 mg oxycodone HCl), 27 mg (equivalent to 30 mg oxycodone HCl), and 36 mg (equivalent to 40 mg oxycodone HCl) capsules. The capsule strengths describe the amount of oxycodone base per capsule. The structural formula for oxycodone is as follows:



$C_{18}H_{21}NO_4$ MW 315.37 g/mol

The chemical name is 4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one.

Oxycodone base is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone is present as myristate salt in the XTAMPZA ER formulation.

Each XTAMPZA ER capsule contains either 9, 13.5, 18, 27, or 36 mg of oxycodone (equivalent to 10, 15, 20, 30, or 40 mg of oxycodone HCl, respectively) and the following inactive ingredients: myristic acid, yellow beeswax, carnauba wax, stearoyl polyoxyl-32 glycerides, magnesium stearate, and colloidal silicon dioxide. The capsule shells collectively contain titanium dioxide, hypromellose, and water. Additionally, the 9 mg and 18 mg strength capsule shells contain yellow iron oxide, the 13.5 and 36 mg strength capsule shells contain red iron oxide, and the 27 mg strength capsule shells contain black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug. In addition, when oxycodone binds to mu-opioid receptors, it results in positive subjective effects, such as drug liking, euphoria, and high.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of

the brain stem respiratory centers to both increases in CO_2 tension and to electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations *[see Overdosage (10)]*.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective "drug effect," analgesia, and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.5)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

12.3 Pharmacokinetics

The activity of XTAMPZA ER is primarily due to the parent drug oxycodone. XTAMPZA ER is designed to provide delivery of oxycodone over 12 hours.

Absorption

XTAMPZA ER is not bioequivalent to oxycodone extended-release tablets. In the fasted state, both peak serum concentration (C_{max}) and extent of absorption (AUC) are lower for XTAMPZA ER, and in the fed state, C_{max} is lower, but AUC is similar.

Compared to immediate-release oxycodone solution dosed under fasted conditions the mean C_{max} of oxycodone from XTAMPZA ER is lower (73% and 43% lower for fasted and fed administration, respectively) and the median time to peak plasma concentration (T_{max}) is approximately 3 hours longer. The extent of absorption of oxycodone from XTAMPZA ER is less than from immediate-release oxycodone oral solution in the fasted state (relative bioavailability of 75%), but comparable in the fed state (relatively bioavailability of 114%).

The peak plasma concentration of oxycodone from XTAMPZA ER occurs approximately 4.5 hours after fed dose administration. Upon repeated dosing with XTAMPZA ER in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half life ($t_{½}$) of oxycodone following the administration of XTAMPZA ER when dosed in the fed state was 5.6 hours compared to 3.2 hours for immediate-release oxycodone.

Food Effects

The oral bioavailability of oxycodone from XTAMPZA ER is greater when taken with food than when taken in the fasted state. The oral bioavailability is dependent on the food consumed and is greatest following a high-fat and high-calorie meal with an increase in C_{max} of 100-150% and AUC of 50-60% compared to the fasted state. Following a medium-fat medium-calorie meal, the C_{max} increased by 84% and AUC by 28% compared to the fasted state. Following a low-fat low-calorie meal, C_{max} was 19% higher and AUC was comparable, relative to the fasted state.

Pharmacokinetic Profile of XTAMPZA ER Intact and Sprinkled

Plasma concentration over time has been measured following administration of XTAMPZA ER capsule contents intact with food and sprinkled. The pharmacokinetic profile for the capsule contents sprinkled was equivalent to intact capsule administration (Table 8).

Table 8: Oxycodone Pharmacokinetic Parameters, Administration of Capsule Contents and Intact Capsules (36 mg)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}INF}$ (hr•ng/mL)
Intact XTAMPZA ER Capsules (fed)	55.3 (13.6)	4.5 (1.5 – 9.0)	540 (143)
Sprinkled XTAMPZA ER Capsule Contents (fed)	48.1 (12.0)	4.5 (2.5 – 9.0)	528 (130)

Values shown for C_{max} and $AUC_{0\text{-}INF}$ are mean (standard deviation); values shown for T_{max} are median (minimum – maximum).

Distribution

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.2)]*.

Elimination

In humans, oxycodone is extensively metabolized. Oxycodone and its metabolites are excreted primarily via the kidney.

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone, and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6-mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7)]*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone; however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and to possess analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol, and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Age: Geriatric Population

The plasma concentrations of oxycodone are nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Sex

Across individual pharmacokinetic studies, oxycodone plasma exposures for female subjects were up to 20% higher than for male subjects, even after considering differences in body weight or BMI. The reason for this difference is unknown *[see Use in Specific Populations (8)]*.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for

oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation, but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination $t_{½}$ for oxycodone of 1 hour.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. The mean elimination $t_{½}$ for oxycodone increased by 2.3 hours.

Drug Interaction Studies

CYP3A4 Inhibitors

CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of a 10 mg single dose of oxycodone extended-release tablet and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7)]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade is not expected to be of clinical significance for XTAMPZA ER *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone was genotoxic in the *in vitro* mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the *in vitro* chromosomal aberration assay, the *in vitro* bacterial reverse mutation assay (Ames test), and the *in vivo* bone marrow micronucleus assay in mice.

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone HCl did not affect reproductive function in male or female rats at any dose tested (≤8 mg/kg/day), up to 1.3 times a human dose of 60 mg/day.

13.2 Animal Toxicology

The safety of beeswax, carnauba wax, and myristic acid in XTAMPZA ER in doses exceeding a total daily dose of 288 mg oxycodone per day (equivalent to 320 mg oxycodone HCl per day) has not been studied.

14 CLINICAL STUDIES

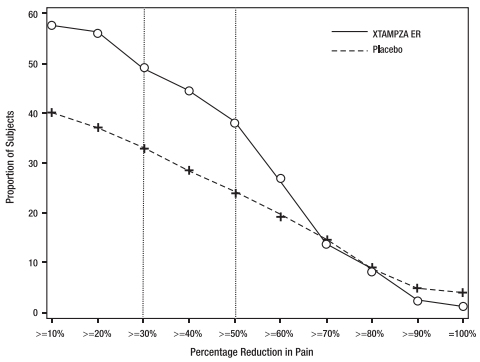
An enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study was conducted in 740 patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy. During screening, patients stopped their prior opioid analgesics and/or non-opioid analgesics prior to starting XTAMPZA ER treatment. Patients were titrated to a stable and tolerated dose between 18 mg (equivalent to 20 mg oxycodone HCl) twice daily and 72 mg (equivalent to 80 mg oxycodone HCl) twice daily of XTAMPZA ER in an open-label fashion during the first six weeks of the trial. Optional use of rescue medication (acetaminophen 500 mg tablets) up to 2 tablets every 4-6 hours was permitted during the dose titration phase, up to 2000 mg per day. XTAMPZA ER was titrated once every three to seven days until a stable and tolerable dose was identified (maximum dose of 72 mg [equivalent to 80 mg oxycodone HCl] twice daily).

Following the titration phase, 389 subjects (53%) met the study randomization criteria of adequate analgesia (pain reduction of at least 2 points from screening baseline to a score of 4 or less on a 0-10 numerical rating scale) and acceptable tolerability of XTAMPZA ER and entered the randomized, double-blind maintenance phase. Subjects discontinued from the dose-titration phase for the following reasons: failure to meet entrance criteria (18%), adverse events (13%), subject request (7%) and lack of efficacy (5%). Patients were randomized at a ratio of 1:1 into a 12-week double-blind maintenance phase with their fixed stable dose of XTAMPZA ER (or matching placebo). Patients randomized to placebo were given a blinded taper of XTAMPZA ER according to a prespecified tapering schedule; XTAMPZA ER was decreased by 25% to 35% every 5 days for the higher doses of XTAMPZA ER and up to 50% every 5 days for the mid-to-lower doses of XTAMPZA ER over the first 20 days of the double-blind maintenance phase. Patients were allowed to use rescue medication (acetaminophen 500 mg tablets) up to a maximum dose of 2000 mg per day. During the double-blind maintenance phase, 122 patients (63%) completed the 12-week treatment with XTAMPZA ER and 100 (51%) completed with placebo. Overall, 11% of patients discontinued due to lack of efficacy (4% of XTAMPZA ER patients and 17% of placebo patients), and 7% discontinued due to adverse events (7% of XTAMPZA ER patients and 7% of placebo patients).

In this study, there was a significant difference in pain reduction, favoring XTAMPZA ER, between XTAMPZA ER (doses of 36-144 mg per day, equivalent to 40-160 mg of oxycodone HCl) and placebo, based on the primary endpoint of change in average pain intensity from randomization baseline to Week 12 of the double-blind maintenance phase.

The proportion of patients (responders) in each group who demonstrated improvement in their weekly average pain scores from screening baseline to Week 12, is shown in Figure 2. The figure is cumulative, so that patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were classified as non-responders. Treatment with XTAMPZA ER resulted in a higher proportion of responders, defined as patients with at least a 30% and 50% improvement as compared to placebo.

Figure 2: Responder Analysis for Pain Intensity: Percent Reduction/Improvement (Intent-to-Treat Population)



16 HOW SUPPLIED/STORAGE AND HANDLING

XTAMPZA ER capsules are supplied in 100-count bottles with a child-resistant closure and as a hospital unit dose package with 10 individually blistered capsules per card; two cards per carton as follows:

Table 9: Summary of XTAMPZA ER Capsule Strengths and Packaging Configurations

Strength	Capsule Description	NDC Number (100-count Bottles with a child-resistant closure)	NDC Number (20-count Hospital Unit Dose Blister Cartons)
9 mg (equivalent to 10 mg oxycodone HCl)	Size 3, ivory cap printed with "XTAMPZA ER" and white body printed with "9 mg"	NDC 24510-110-10	NDC 24510-110-20
13.5 mg (equivalent to 15 mg oxycodone HCl)	Size 2, Swedish orange cap printed with "XTAMPZA ER" and white body printed with "13.5 mg"	NDC 24510-115-10	NDC 24510-115-20
18 mg (equivalent to 20 mg oxycodone HCl)	Size 1, rich yellow cap printed with "XTAMPZA ER" and white body printed with "18 mg"	NDC 24510-120-10	NDC 24510-120-20
27 mg (equivalent to 30 mg oxycodone HCl)	Size 0, light gray cap printed with "XTAMPZA ER" and white body printed with "27 mg"	NDC 24510-130-10	NDC 24510-130-20
36 mg (equivalent to 40 mg oxycodone HCl)	Size 00, flesh color cap printed with "XTAMPZA ER" and white body printed with "36 mg"	NDC 24510-140-10	NDC 24510-140-20

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container, with child-resistant closure.

Store XTAMPZA ER securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide)*.

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store XTAMPZA ER securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving XTAMPZA ER unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]*.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused XTAMPZA ER should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of XTAMPZA ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share XTAMPZA ER with others and to take steps to protect XTAMPZA ER from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression including information that the risk is greatest when starting XTAMPZA ER or when the dosage is increased, and that it can occur even at recommended dosages.

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 *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if XTAMPZA ER is used with benzodiazepines or other CNS depressants, including alcohol, (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids), and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that the effects of opioid overdose reversal agents like naloxone and nalmefene are temporary, and that they must call 911 or get emergency medical help right away in cases of known or suspected opioid overdose, even if an opioid overdose reversal agent is administered *[see Overdosage (10)]*.

Advise patients and caregivers:

- how to treat with the overdose reversal agent in the event of an opioid overdose.
- to tell family and friends about the opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency.
- to read the Patient Information (or other educational material) that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.7), Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that XTAMPZA ER could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking XTAMPZA ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking XTAMPZA ER *[see Drug Interactions (7)]*.

Food Effect

Because food has an effect on absorption of oxycodone from XTAMPZA ER, each dose of XTAMPZA ER should be taken with food in order to ensure that appropriate plasma levels are consistently achieved. Instruct patients to take XTAMPZA ER with approximately the same amount of food regardless of whether they swallow the capsule whole or sprinkle on soft food or into a cup and then administer directly into the mouth.

XTAMPZA ER may be taken as intact capsules or, alternately, may be administered 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 *[see Dosage and Administration (2.1, 2.7)]*.

Important Administration Instructions

[see Dosage and Administration (2.1, 2.6, 2.7), Warnings and Precautions (5.2)]

Instruct patients how to properly take XTAMPZA ER, including the following:

- Taking XTAMPZA ER with food
- Swallowing XTAMPZA ER capsules whole or sprinkling the capsule contents on soft food or into a cup and administering directly into the mouth
- Using XTAMPZA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue XTAMPZA ER without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.6)]*.

Driving or Operating Heavy Machinery

Inform patients that XTAMPZA ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.15)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Adrenal Insufficiency

Inform patients that XTAMPZA ER could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.9)]*.

Hypotension

Inform patients that XTAMPZA ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.10)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in XTAMPZA ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of XTAMPZA ER for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryofetal Toxicity

Advise females of reproductive potential that XTAMPZA ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with XTAMPZA ER *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

Healthcare professionals can telephone Collegium Pharmaceutical's Medical Affairs Department (1-855-331-5615) for information on this product.

Manufactured by: Patheon Pharmaceuticals, Cincinnati, OH 45237

U.S. Patent Nos. 7,399,488; 7,771,707; 8,449,909; 8,557,291; 8,758,813; 8,840,928; 9,044,398; 9,248,195; 9,592,200; 9,682,075; 9,737,530; 9,763,883; 9,968,598; 10,004,729; 10,188,644; 10,525,052; 10,525,053; 10,646,485; and 10,668,060

COL-010

Medication Guide

XTAMPZA® ER (ex tamp' zah ee ar)
(oxycodone) extended-release capsules, CII

XTAMPZA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage severe and persistent pain that requires an extended treatment period with a daily opioid medicine, when other pain medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed by your healthcare provider, you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not to be taken on an "as needed" basis

Important information about XTAMPZA ER:

- **Get emergency help or call 911 right away if you take too much XTAMPZA ER (overdose).** When you first start taking XTAMPZA ER, when your dose is changed, or if you take too much (overdose), serious life threatening breathing problems that can lead to death may occur. Ask your healthcare provider about medicines like naloxone or nalmefene that can be used in an emergency to reverse an opioid overdose.
- Taking XTAMPZA ER with other opioid medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Taking XTAMPZA ER with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your XTAMPZA ER. They could die from taking it. Selling or giving away XTAMPZA ER is against the law.
- Store XTAMPZA ER securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take XTAMPZA ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking XTAMPZA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose or mental health problems.Tell your healthcare provider if you are:
- **noticing your pain getting worse.** If your pain gets worse after you take XTAMPZA ER, do not take more of XTAMPZA ER without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking XTAMPZA ER.
- **pregnant or planning to become pregnant.** Use of XTAMPZA ER for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with XTAMPZA ER. It may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking XTAMPZA ER with certain other medicines can cause serious side effects that could lead to death.

When taking XTAMPZA ER :

- Do not change your dose. Take XTAMPZA ER exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours, at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- If you cannot swallow XTAMPZA ER capsules, see the detailed Instructions for Use.
- Always take XTAMPZA ER capsules with approximately the same amount of food to ensure enough medicine is absorbed.
- Swallow XTAMPZA ER whole. Do not snort or inject XTAMPZA ER because this may cause you to overdose and die.
- The contents of the XTAMPZA ER capsules may be sprinkled on soft food, sprinkled into a cup and then put directly into the mouth, or given through a nasogastric or gastrostomy tube.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking XTAMPZA ER without talking to your healthcare provider.**
- Dispose of expired, unwanted, or unused XTAMPZA ER by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking XTAMPZA ER DO NOT:

- Drive or operate heavy machinery, until you know how XTAMPZA ER affects you. XTAMPZA ER can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with XTAMPZA ER may cause you to overdose and die.

The possible side effects of XTAMPZA ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion

These are not all the possible side effects of XTAMPZA ER. Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. **For more information, go to** dailymed.nlm.nih.gov

Manufactured by: Patheon Pharmaceuticals, 2110 Galbraith Road, Cincinnati, OH 45237, www.collegiumpharma.com or call 855-331-5615

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: December 2025

Instructions for Use

XTAMPZA® ER (ex tamp' zah ee ar)
(oxycodone) extended-release capsules, CII

Always take XTAMPZA ER with approximately the same amount of food. If you cannot swallow XTAMPZA ER capsules, tell your healthcare provider. If your healthcare provider tells you that you can take XTAMPZA ER by sprinkling the capsule contents, follow these steps:

XTAMPZA ER can be opened and the contents inside the capsule can be sprinkled onto soft foods (such as, applesauce, pudding, yogurt, ice cream, or jam) as follows:

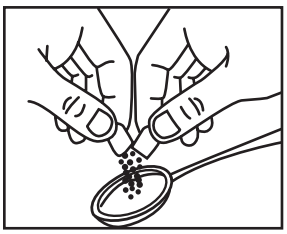


Figure 1

- Open the XTAMPZA ER capsule and sprinkle the contents over about one tablespoon of the soft food listed above (See Figure 1).

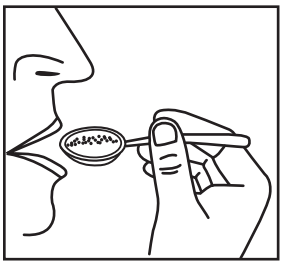


Figure 2

- Swallow all of the soft food and sprinkled capsule contents right away. Do not save any of the soft food and capsule contents for another dose (See Figure 2).

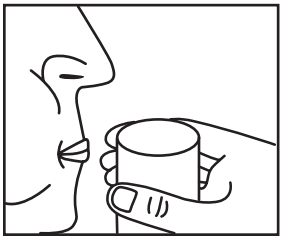


Figure 3

- Rinse your mouth to make sure you have swallowed all of the capsule contents. (See Figure 3).

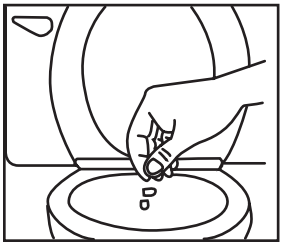


Figure 4

- Flush the empty capsule down the toilet right away (See Figure 4).

XTAMPZA ER capsule contents can also be sprinkled into a cup and then put directly into the mouth.

<u>Giving XTAMPZA ER through a nasogastric or gastrostomy tube:</u>

<u>Use water, milk, or a liquid nutritional supplement to flush the tube when giving XTAMPZA ER.</u>

Step 1: Flush the nasogastric or gastrostomy tube with liquid.

Step 2: Open an XTAMPZA ER capsule and carefully pour the contents of the capsule directly into the tube. **Do not** pre-mix the capsule contents with the liquid used to flush the capsule contents through the tube.

Step 3: Draw up 15 mL of liquid into a syringe, insert the syringe into the tube, and flush the contents of the capsule through the tube to give the dose.

Step 4: Flush the tube two more times, each time with 10 mL of liquid, to ensure that none of the contents of the capsule are left in the tube.

This Instruction for Use has been approved by the U.S. Food and Drug Administration. Issued: December 2025

COL-007

Collegium PHARMACEUTICAL