Oxycodone extended-release (Xtampza ER™) Abbreviated New Drug Update (ANDU)

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OVERVIEW[1,2]

- Oxycodone extended-release capsule (Xtampza ER), a Schedule II controlled substance, is a full opioid agonist selective for mu receptors (but capable of binding to other receptors at higher doses) indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options in patients 18 years and older are inadequate. Xtampza ER employs a proprietary DETERx® technology designed to prevent tampering.
  - ❒ DETERx technology uses a microsphere-in-capsule formulation. In each microsphere, oxycodone is present as a solid solution of a fatty acid salt (oxycodone myristate) in a hydrophobic matrix that also contains waxes resulting in the drug's extended-release and abuse-deterrent properties.
  - ❒ Limitation of use: Because of the potential for addition, abuse or misuse even at recommended doses coupled with increased risks of overdose and death when using extended-release opioids, this should be reserved for patients without alternative treatment options to long-acting opioids. It is not to be used on an as needed basis.
- Contraindications/Warnings
  - ❒ Contraindications: Known hypersensitivity to oxycodone; significant respiratory depression; acute or severe bronchial asthma; and known or suspected gastrointestinal obstruction (including paralytic ileus).
  - ❒ Boxed warnings: Similar to other opioid products these include addiction, abuse, and misuse; life-threatening respiratory depression; accidental exposure/ingestion; concomitant use with a P450 inducer or inhibitor; and neonatal opioid withdrawal syndrome.
  - ❒ Other warnings: Severe hypotension, sedation and possible death in patients concomitantly using other central nervous system (CNS) depressant medications (e.g. benzodiazepines, sedative hypnotics, anxiolytics, anesthetics, tranquilizers, antipsychotics along with other opioids);; adrenal insufficiency; orthostatic hypotension and syncope; overdose in moderate to severe hepatic impairment; hypersensitivity; seizures in susceptible patients; withdrawal; impairment while driving/operating heavy machinery; and limitations in accurate urine drug screening.
- Availability
  - ❒ Extended-release capsules: 9, 13.5, 18, 27, and 36 mg.
- Dosage and Administration

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- ❒ Opioid-naïve: 9 mg orally every 12 hours taken with food. Monitor for respiratory depression especially during the first 24 to 72 hours and after dosage increases. Adjustments in dosing are recommended to occur no earlier then every 1 to 2 days.
- ❒ Opioid-experienced: Single doses of 36 mg or greater and total daily doses of 72 mg and greater should be reserved for patients whom have shown tolerance for comparable opioid potency analgesia. The maximum daily dose is 288 mg (320 mg oxycodone HCl per day).
- ❒ Conversion: Patients receiving other oxycodone products may convert on the basis of administering one-half of the current daily dose every 12 hours with Xtampza ER. For other opioids, discontinue the current opioid analgesia, and initiate typically with a 9 mg dose and titrate as required. If changing from fentanyl transdermal, it is recommended to wait 18 hours until the first dose of Xtampza ER. Close monitoring is recommended when changing from methadone due to the long half-life of methadone.

Xtampza ER Dose	Oxycodone HCl Equivalents
9 mg	10 mg
13.5 mg	15 mg
18 mg	20 mg
27 mg	30 mg
36 mg	40 mg

- ❒ Reduced doses of one-third to one-half should be used for patients with severe hepatic impairment along with close monitoring for adverse events.
- ❒ Administer every 12 hours with food; may sprinkle capsule contents onto food or in a cup for administration by mouth, nasogastric tube, or gastronomy tube.

- Adverse Events
  - ❒ Incidence ≥ 5%: nausea, constipation, headache, constipation, somnolence, pruritus, vomiting, and dizziness.
- Drug Interactions
  - ❒ Concomitant use of CYP3A4 and CYP2D6 inhibitors or discontinuing CYP3A4 inducers (e.g., ketoconazole, erythromycin, carbamazepine, phenytoin, rifampin); monitor and adjust Xtampza ER dosage as required if concomitant use is warranted.
  - ❒ Concomitant use of benzodiazepines, muscle relaxants and other CNS depressants may increase risk of respiratory depression, profound sedation, and death; consider a dose reduction for one or both drugs.
  - ❒ Concomitant use of partial opioid agonists or mixed agonist/antagonists; may precipitate withdrawal or reduce analgesia.
  - ❒ Concomitant use of diuretics and anticholinergics may reduce the efficacy of the diuretic and increase the risk of urinary retention respectively; monitor and adjust the doses as needed.

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- Clinical Trials
  - An enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group study assessed the efficacy of Xtampza ER in 740 patients with persistent, moderate-to-severe chronic lower back pain and inadequate pain control on previous therapy. Prior opioid and/or non-opioid analgesics were discontinued, and patients were titrated to a stable and tolerable dose of Xtampza ER (maximum 72 mg twice daily; titrated every 3 to 7 days) during a 6-week, open-label, dose-optimization phase. During the initial titration phase, 13% of subjects discontinued treatment due to adverse effects while 5% discontinued due to lack of efficacy. Patients with adequate analgesia (pain ≤ 4 on a 0 to 10 pain scale and reduction of ≥ 2 points) and tolerability then entered a randomized, double-blind, 12-week, maintenance phase (n=389). Patients were randomized 1:1 to switch to placebo with a dose-tapering schedule of up to 20 days or to continue Xtampza ER. Rescue medication with acetaminophen (maximum 2 g/day) was permitted during both the titration and the double-blind phase. The primary endpoint, change in average pain intensity from randomization baseline scores to week 12 of the double-blind maintenance phase, was higher in those taking Xtampza ER compared to placebo (data not provided). During the double-blind phase, 63% of those assigned Xtampza ER compared to 51% of those assigned placebo completed the 12-week treatment. In the Xtampza ER group, 4% discontinued due to lack of efficacy and 7% discontinued due to adverse effects compared to 17% and 7%, respectively, in the placebo group.
  - Both *in vitro* and *in vivo* abuse potential studies have been conducted. Oral abuse and nasal abuse clinical studies were performed and indicate that properties of Xtampza ER limit abuse potential; however, abuse is still possible.

CLINICAL CONSIDERATIONS[3,4,5,6,78]

- Oral long-acting opioids include extended-release hydrocodone (Hysingla® ER, Zohydro® ER), extended-release hydromorphone (Exalgo®), methadone (Dolophine®), extended-release morphine sulfate (Kadian®), controlled-release morphine sulfate (MS Contin®), extended-release morphine sulfate/naltrexone (Embeda®, MorphaBond™), controlled-release oxycodone (OxyContin®), extended-release oxymorphone (Opana® ER), extended-release tapentadol (Nucynta® ER), and extended-release tramadol (ConZip®, Ultram® ER). Transdermal long-acting opioids include buprenorphine (Butrans®) and fentanyl (Duragesic®). Buccal buprenorphine (Belbuca™) is also available.
- The World Health Organization's (WHO) guidelines for cancer pain management and American Pain Society's guidelines for the use of chronic opioid therapy for the treatment of chronic non-cancer pain do not recommend one long-acting opioid over another. Likewise, a 2009 evidence review performed by the American Pain Society in conjunction with the American Academy of Pain Medicine did not identify any significant differences in the benefit or harm of extended-release opioids and related products in the treatment of chronic non-cancer pain. A position statement released by the American Academy of Neurology (AAN) states that the risks of opioids outweigh their benefits for treating chronic non-cancer pain.
- Guidelines recently released by the Centers for Disease Control and Prevention (CDC) urge the use of non-opioid analgesia, except in cases of cancer pain, and recommend use of the lowest

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dosage possible for as short of a time as possible to prevent continued increases in addiction and opioid misuse.

- Collegium's Xtampza ER, an extended-release oxycodone capsule, offers another abuse-deterrent long-acting opioid option for adults with chronic pain.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Long Acting Narcotic Analgesics
Clinical Edit	Prior authorization will be required if product is determined to be non-preferred Patient must: ▪ Have diagnosis of moderate to severe chronic pain requiring around the clock opioid analgesia; **AND** ▪ Be 18 years old or older; **AND** ▪ Have no history of opioid abuse or illicit drug use within the past 365 days; **AND** ▪ Trial and failure of two different preferred long acting narcotics; **OR** ▪ Patient's pain is controlled currently on this formulation; **OR** ▪ Patient has current history of extended-release oxycodone use for previous opioid dependence and requires chronic pain management.
Quantity Limit	60 capsules/1 month
Duration of Approval	6 months
Drug to Disease Hard Edit	None

REFERENCES

1 Xtampza ER [package insert]. Cincinnati, OH; Collegium; April 2016.
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