
Drug Monograph

Generic Name: oxycodone extended-release

Trade Name: Xtampza ER[®]

Dosage Form: Extended-release capsules

NDCs: 24510-0110-10, 24510-0115-10, 25410-0120-10, 25410-0130-10, 24510-0140-10

Manufacturer: Collegium Pharmaceutical, Inc.

ADF Product Classification: Physical/Chemical Barrier

Executive Summary

Xtampza ER[®] (oxycodone extended-release) is Food and Drug Administration (FDA)-approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This agent, like other long-acting opioids, should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Xtampza ER[®] (oxycodone extended-release) is dosed every 12 hours with food, and the contents of the capsule may be sprinkled onto soft food for individuals that may have difficulty swallowing the capsules.¹ Xtampza ER[®] (oxycodone extended-release) is being evaluated by the Drug Formulary Commission, as it is a relatively new FDA-labeled abuse-deterrent formulation (ADF) in the marketplace to be considered for inclusion on the Massachusetts formulary of interchangeable abuse-deterrent drugs, as outlined in Chapter 258 of the Acts of 2014.

Xtampza ER[®] (oxycodone extended-release) was approved by the FDA pursuant to a 505(b)(2) New Drug Application with OxyContin[®] (oxycodone extended-release) as the reference product; however, the efficacy and safety of Xtampza ER[®] (oxycodone extended-release) was evaluated in a phase III clinical trial. The clinical trial was an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study conducted in patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy (n=740). Following a titration phase, 389 subjects were randomized to either Xtampza ER[®] (oxycodone extended-release) or placebo for 12 weeks. After 12 weeks, there was a significant difference in pain reduction (0.29 vs. 1.85 ;P<0.0001), favoring Xtampza ER[®] (oxycodone extended-release), based on the primary endpoint of change in average pain intensity from randomization baseline to Week 12.^{2,3}

Xtampza ER[®] (oxycodone extended-release) capsules utilize DETERx[®] technology to impart abuse-deterrent properties. The capsules contain microspheres that consist of oxycodone myristate, which is a lipophilic compound produced by forming a salt of oxycodone with myristic acid. This lipophilic compound is then distributed into waxes to form microspheres to further limit the solubility of the oxycodone in water. *In vitro* manipulation and extraction studies reveal that Xtampza ER[®] (oxycodone extended-release) is resistant to particle size reduction using most tools, extraction of oxycodone via the use of a panel of solvents was relatively low, passage through commonly used needle sizes for intravenous (IV) injection is not possible and IV delivery of molten Xtampza ER[®] (oxycodone extended-release) is not possible.^{2,4,5}

In addition to *in vitro* manipulation and extraction studies, Xtampza ER[®] (oxycodone extended-release) was evaluated in clinical abuse potential studies for both the oral and intranasal routes. In the oral clinical abuse potential study, drug liking scores for crushed Xtampza ER[®] (oxycodone extended-release) microspheres taken orally were significantly lower than for oxycodone IR, and equivalent to drug liking scores for intact Xtampza ER[®] (oxycodone extended-release). Evaluation of willingness to take drug again revealed no significant differences in the oral clinical abuse potential study. The intranasal clinical abuse potential study revealed that both drug liking and willingness to take drug again scores were significantly lower for crushed Xtampza ER[®] (oxycodone extended-release) than crushed oxycodone IR.^{2,6}

Reference Data

Xtampza ER[®] (oxycodone extended-release) is a long-acting formulation of oxycodone. Oxycodone is an opioid agonist that is relatively selective for the μ opioid receptors; although, other opioid receptor subtypes may be stimulated at higher doses.¹ Stimulation of the μ opioid receptors results in analgesia, decreased gastrointestinal motility, euphoria, physical dependence, respiratory depression and sedation.⁷ The abuse-deterrent properties of Xtampza ER[®] (oxycodone extended-release) are unique relative to other abuse-deterrent formulations. Oxycodone and myristic acid are combined to form oxycodone myristate, which is a lipophilic compound that is then dissolved in waxes to form microspheres that are resistant to solubility in water and other solvents. The wax microspheres in Xtampza ER[®] (oxycodone extended-release) capsules are resistant to particle size reduction using various tools, and are not able to pass through needle sizes used by IV drug users. Passage of crushed Xtampza ER[®] (oxycodone extended-release) microspheres through an 18 gauge needle was possible; however, the uptake was less than 15% of the fill weight of the capsule and an 18 gauge needle would be undesirable for IV injection due to the large size.²

Table 1. Long-Acting Opioid Availability^{8,9}

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Buprenorphine (Belbuca [®] , Butrans [®])	-	✓
Fentanyl (Duragesic [®])	-	✓
Hydrocodone (Hysingla ER [®])	✓	✓
Hydrocodone (Zohydro ER [®])	-	✓
Hydromorphone (Exalgo [®])	-	✓
Levorphanol (Levo-Dromoran [®])	-	✓
Methadone (Diskets Dispersible [®] , Dolophine [®] , Methadose [®] , Methadone Intenso [®])	-	✓
Morphine sulfate (Avinza [®] , Kadian [®] , MS Contin [®])	-	✓
Morphine sulfate (MorphaBond [®])	✓	-
Morphine sulfate/naltrexone (Embeda [®])	✓	✓
Oxycodone (OxyContin [®])	✓	✓
Oxycodone (Xtampza ER [®])	✓	✓
Oxycodone/naloxone (Targiniq ER [®])	✓	-
Oxymorphone (Opana [®] ER)	-	✓
Tapentadol (Nucynta ER [®])	-	✓

Therapeutic Indications/Efficacy

The safety and efficacy of Xtampza ER[®] (oxycodone extended-release) was evaluated in an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study that was conducted in patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy (n=740). 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[®] (oxycodone extended-release) in an open-label fashion during the first six weeks of the trial. Xtampza ER[®] (oxycodone extended-release) 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 ≥ 2 points from screening baseline to a score of ≤ 4 on a 0 to 10 numerical

rating scale) and acceptable tolerability and entered the randomized, double-blind maintenance phase. 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[®] (oxycodone extended-release) or matching placebo. In this study, there was a significant difference in pain reduction (0.29 vs. 1.85 ; $P < 0.0001$), favoring Xtampza ER[®] (oxycodone extended-release) compared to placebo, based on the primary endpoint of change in average pain intensity from randomization baseline to Week 12. An assessment of secondary outcomes demonstrated that the Xtampza ER[®] (oxycodone extended-release) group, compared to placebo, had more subjects with significant improvement in patient global impression of change ($P < 0.0001$), longer time-to-exit from the study ($P < 0.0102$), and a greater proportion of patients with $>30\%$ ($P = 0.0013$) and $>50\%$ ($P = 0.0032$) improvement in pain intensity.¹⁻³

Xtampza ER[®] (oxycodone extended-release) was evaluated for abuse potential in *in vitro* laboratory manipulation and extraction studies and two randomized, double-blind, placebo and positive-controlled clinical abuse potential studies of the oral and intranasal routes. *In vitro* manipulation and extraction studies examined particle size reduction, dissolution or extraction in solvents, preparation of Xtampza ER[®] (oxycodone extended-release) microspheres for IV injection and simulated smoking. In the study assessing particle size reduction, ten common household tools were tested for their ability to reduce the particle size of Xtampza ER[®] (oxycodone extended-release) microspheres. Only two of the ten tools produced particle size reduction of any significance, and these tools were able to reduce the particle size of the microspheres by 17.8% and 12.8%. In comparison, particle size reduction of OxyContin[®] (oxycodone extended-release) was possible using seven of ten tools. Particle size reduction of a “notable magnitude” was achieved using six of the ten tools with OxyContin[®] (oxycodone extended-release).^{2,4}

After determining the most effective method of particle size reduction, a study was conducted to assess the ability to prepare the manipulated and intact Xtampza ER[®] (oxycodone extended-release) microspheres for intravenous injection with crushed and intact OxyContin[®] (oxycodone extended-release) and oxycodone IR as comparators. Water was added to the samples in volumes of 5 mL and 10 mL at room temperature and at 90 to 95°C with agitation over 5, 15 and 30 minute extraction periods. The highest amount of oxycodone extracted from Xtampza ER[®] (oxycodone extended-release) over 30 minutes was 11.2% of a manipulated 40 mg dosage unit under heated conditions in 10 mL of water. In comparison, 47% of a manipulated 40 mg dosage unit of OxyContin[®] (oxycodone extended-release) was extracted under the same conditions, and 98.2% of oxycodone was extracted from oxycodone IR at room temperature in 10 mL of water. A suspension of intact Xtampza ER[®] (oxycodone extended-release) microspheres was unable to pass through a 27-gauge needle, trace amounts of oxycodone (0.03% original weight) passed through a 22-gauge needle and less than 13.6% was able to pass through an 18-gauge needle. Manipulated Xtampza ER[®] (oxycodone extended-release) microspheres in suspension yielded similar results, with a maximum of 12.6% original weight of oxycodone able to pass through an 18-gauge needle. Melting microspheres for passage through an 18-gauge needle resulted in microsphere solidification within the needle almost instantly.⁵

Studies were performed to determine the ability of solvents to extract oxycodone from intact and manipulated Xtampza ER[®] (oxycodone extended-release) microspheres, intact and manipulated OxyContin[®] (oxycodone extended-release) and intact and manipulated oxycodone immediate-release. Products were crushed using the most effective tools that were able to reduce particle size. Seven common ingestible solvents were used to attempt to enhance the extraction of oxycodone from Xtampza ER[®] (oxycodone extended-release) microspheres over an eight hour period with continuous agitation. Intact formulations released ingredient consistent with their expected release profiles. One solvent was able to extract 77% of the oxycodone in manipulated Xtampza ER[®] (oxycodone extended-release) microspheres after eight hours; however, all other solvents extracted less than 40%. In comparison, four solvents extracted over 90% of oxycodone from manipulated OxyContin[®] (oxycodone extended-release) after eight hours.²

Xtampza ER[®] (oxycodone extended-release) was evaluated for abuse potential by smoking via an *in vitro*, laboratory simulated smoking study at various temperatures. At the highest temperature evaluated,

vapor was collected over a five minute smoking period for Xtampza ER[®] (oxycodone extended-release), OxyContin[®] (oxycodone extended-release) and oxycodone IR to measure the amount of the label dose of oxycodone was present in the vapor. A similar amount of the label dose of oxycodone was released in the vapor at the highest temperature evaluated with 51%, 36% and 43% released, respectively.²

The clinical abuse potential of Xtampza ER[®] (oxycodone extended-release) was evaluated in clinical abuse potential studies of the intranasal and oral routes. The oral clinical abuse potential study (CP-24) was a double-blind, randomized, placebo-controlled, single dose crossover study in 41 nondependent recreational opioids abusers. Chewed and intact Xtampza ER[®] (oxycodone extended-release) administered in fed and fasted states were compared to oxycodone IR in the fasted state. The primary endpoint was the peak “Drug Liking” on the Drug Effects Questionnaire Visual Analogue Scale (DEQ-VAS), where 0 is strong disliking and 100 is strong liking. Secondary endpoints evaluated were DEQ-VAS scores for “Take Drug Again”, “Good Effects”, “Feeling High”, “Bad Effects”, “Sick”, “Nausea”, “Sleepy”, “Any Effects”, Addiction Research Center Inventory/Morphine Benzidine Group (ARCI/MBG) questionnaire scores, and “Overall Drug Liking”. Peak Drug Liking for both chewed and intact Xtampza ER[®] (oxycodone extended-release) was significantly lower than peak Drug Liking for oxycodone IR ($P < 0.0001$). VAS scores for Good Effects, Feeling High, and Any Effects were significantly lower for Xtampza ER[®] (oxycodone extended-release) than oxycodone IR ($P < 0.0001$). ARCI/MBG scores were significantly lower for Xtampza ER[®] (oxycodone extended-release) compared to oxycodone IR ($P < 0.01$). VAS scores for Overall Drug Liking were significantly lower for chewed Xtampza ER[®] (oxycodone extended-release) with a high-fat and high-calorie (HFHC) meal, intact Xtampza ER[®] (oxycodone extended-release) fasted and intact Xtampza ER[®] (oxycodone extended-release) with a HFHC meal ($P < 0.05$, $P < 0.05$ and $P < 0.01$, respectively); however, there was no significant difference in Overall Drug Liking between chewed Xtampza ER[®] (oxycodone extended-release) under fasted conditions and crushed oxycodone IR. VAS scores for Take Drug Again were similar across all groups, indicating that despite less Drug Liking compared to oxycodone IR, participants would still be willing to take Xtampza ER[®] (oxycodone extended-release) again.²

The intranasal abuse potential of Xtampza ER[®] (oxycodone extended-release) was evaluated in a double-blind, randomized, placebo- and positive-controlled, single-dose crossover study in 39 nondependent recreational opioids abusers. Crushed Xtampza ER[®] (oxycodone extended-release) microspheres intranasal, intact Xtampza ER[®] (oxycodone extended-release), crushed oxycodone IR and crushed and intact placebo microspheres were compared. The primary endpoint was comparison of Drug Liking scores on the VAS between crushed Xtampza ER[®] (oxycodone extended-release) intranasal and crushed oxycodone IR intranasal. The secondary endpoints were the comparison of Drug Liking scores on the VAS between crushed Xtampza ER[®] (oxycodone extended-release) intranasal and intact Xtampza ER[®] (oxycodone extended-release) oral and the comparison of Drug Liking scores on the VAS between crushed oxycodone IR intranasal and intact Xtampza ER[®] (oxycodone extended-release) oral. Other endpoints evaluated included VAS scores for “Drug High” and “Good Drug Effects” were also evaluated. The least squares mean difference (LSMD) for Drug Liking between oxycodone IR intranasal and crushed Xtampza ER[®] (oxycodone extended-release) intranasal was 20.69 ($P \leq 0.0001$), indicating that crushed Xtampza ER[®] (oxycodone extended-release) intranasal was liked significantly less. The LSMD between crushed Xtampza ER[®] (oxycodone extended-release) intranasal and intact Xtampza ER[®] (oxycodone extended-release) oral was -5.99 ($P \leq 0.05$), indicating crushed Xtampza ER[®] (oxycodone extended-release) was liked significantly less. The LSMD between oxycodone IR intranasal and intact Xtampza ER[®] (oxycodone extended-release) oral was 14.70 ($P \leq 0.0001$), indicating intact Xtampza ER[®] (oxycodone extended-release) oral was liked significantly less than oxycodone IR intranasal. VAS scores for Drug High, Good Drug Effects and Take Drug Again were significantly lower for crushed Xtampza ER[®] (oxycodone extended-release) intranasal compared to oxycodone IR intranasal ($P < 0.0001$).⁶

Table 2. Clinical Trials^{2,3,6}

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Katz N, et al.³</p> <p>Oxycodone ER capsules 18 mg to 72 mg (equivalent to 20 mg to 80 mg oxycodone HCl) Q12H with food</p> <p>vs</p> <p>placebo</p> <p>All patients were titrated to an individualized dose of oxycodone ER over a titration phase of up to six weeks.</p> <p>At randomization, patients were randomized to continue their dose or a blinded taper to placebo for the 12 week treatment phase.</p>	<p>DB, EE, MC, PC, RCT</p> <p>Patients aged 18 to 75 years with moderate to severe chronic low back pain for a minimum of six months prior to screening. Opioid naïve and opioid experienced (between 30 and 240 mg/day of morphine or equivalent for at least 14 days prior to screening) were included.</p>	<p>N=389</p> <p>12 weeks</p>	<p>Primary: Change in average pain intensity from randomization baseline to Week 12</p> <p>Secondary: SF-12v2, RMDQ scores, PGIC, total amount of rescue medication used</p>	<p>Primary: Mean (SD) pain intensity score from randomization to baseline was significantly lower for oxycodone ER compared to placebo (0.29 [0.15] vs. 1.85 [0.22]; P<0.0001).</p> <p>Secondary: Mean (SD) SF-12v2 score showed a statistically significant increase on the physical component score for oxycodone ER compared to placebo (7.52 [10.13] vs. 3.62 [9.43]; P=0.0016). Mean (SD) SF-12v2 score showed a statistically significant decrease for the mental component score for oxycodone ER compared to placebo (-2.55 [10.42] vs. 0.67 [11.17]; P=0.0362).</p> <p>Mean (SD) RMDQ scores indicated no difference in change in physical disability from randomization baseline to week 12 between oxycodone ER and placebo (0.4 [4.83] vs. 0.7 [5.32]; P=0.4555).</p> <p>PGIC showed a greater proportion of patients in the oxycodone ER group compared to placebo felt they were “very much improved” (26.4% vs. 14.3%) or “improved” (40.4% vs. 32.1%), and the difference was statistically significant (P<0.0001).</p> <p>Mean (SD) number of tablets and mg/day of rescue medication was numerically lower for the oxycodone ER group compared to placebo (0.15 [0.30] vs. 0.23 [0.46] and 144.6 [289.47] vs 189.3 [317.61], respectively)</p>
<p>CP-24²</p> <p>oxycodone ER capsule chewed PO, fasting</p> <p>oxycodone ER capsule chewed PO, fed</p>	<p>DB, PC, SiD, XO, RCT</p> <p>Subjects were nondependent, recreational opioid abusers</p>	<p>N=41</p> <p>Single-dose</p>	<p>Primary: Peak DL scores on DEQ-VAS</p> <p>Secondary: ARCI/MBG, other DEQ-VAS</p>	<p>Primary: Peak DL for both chewed and intact oxycodone ER was significantly lower than for oxycodone IR (P<0.0001).</p> <p>Secondary: ARCI/MGB scores were significantly lower for oxycodone ER compared to oxycodone IR (P<0.01).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxycodone ER capsule PO intact, fasting oxycodone ER capsule PO intact, fed vs oxycodone IR PO, fasting vs placebo	(age range unspecified)		assessments (TDA, “feeling high,” “good effects,” “bad effects,” “overall drug liking,” and “any effects”) and pupil constriction	<p>Scores for “good effects”, “feeling high”, and “any effects” were significantly lower for oxycodone ER than oxycodone IR (P<0.0001).</p> <p>Scores for “overall drug liking” were significantly lower for chewed oxycodone ER with a high-fat and high-calorie meal, intact oxycodone ER, fasted and intact oxycodone ER with a HFHC meal (P<0.05, P<0.05 and P<0.01, respectively); however, there was no significant difference in overall drug liking between chewed oxycodone ER under fasted conditions and crushed oxycodone IR.</p> <p>Subjective assessments corresponded well with a delay in pupil constriction for all oxycodone ER conditions relative to IR oxycodone, as measured by mean pupil diameter.</p> <p>Scores for TDA were similar across all groups, indicating that despite less DL compared to oxycodone IR, participants would still be willing to take oxycodone ER again.</p>
Webster et al. ⁶ oxycodone ER intranasally, crushed vs oxycodone IR intranasally, crushed vs oxycodone ER PO, intact	AC, DB, PC, RCT, SiD, XO Subjects were nondependent, recreational opioid abusers (age range unspecified)	N=39 Single-dose	Primary: DL scores on VAS (oxycodone ER intranasally, crushed vs. oxycodone IR intranasally, crushed) Secondary: DL scores on VAS (oxycodone ER intranasally, crushed vs. oxycodone ER	Primary: The LSMD for Drug Liking between oxycodone IR intranasally, crushed and crushed oxycodone ER intranasally, crushed intranasal was 20.69 (P≤0.0001), indicating that crushed oxycodone ER intranasal was liked significantly less. Secondary: The LSMD between oxycodone ER intranasally, crushed and intact oxycodone ER PO, intact oral was -5.99 (P≤0.05), indicating crushed oxycodone ER intranasally was liked significantly less. The LSMD between oxycodone IR intranasally, crushed and oxycodone ER PO, intact was 14.70 (P≤0.0001), indicating intact oxycodone ER PO was liked significantly less than crushed

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			PO, intact; oxycodone IR intranasally, crushed vs. oxycodone ER PO, intact), VAS scores for TDA, “drug high” and “good drug effects”	oxycodone IR intranasal. VAS scores for Drug High, Good Drug Effects and TDA were significantly lower for oxycodone ER intranasally, crushed intranasal compared to oxycodone IR intranasal, crushed (P<0.0001).

*Trial is registered on ClinicalTrials.gov

Drug regimen abbreviations: Q12H=every twelve hours

Study abbreviations: AC=active controlled, ARCI/MBG= Addiction Research Center Inventory/Morphine Benzedrine Group, CI=confidence interval, DB=double-blind, DEQ-VAS= Drug Effects Questionnaire Visual Analogue Scale, DL=“drug liking”, EE=enriched enrollment, LS=least squares, LSMD=least mean squares difference, MC=multicenter, MOS Sleep-R=Medical Outcome Study Sleep Scale-Revised, PC=placebo-controlled, PoC=positive-controlled, PGIC=Patients’ Global Impression of Change, RCT=randomized controlled trial, SD=standard deviation, SiD=single-dose, TDA=willingness to “take drug again”, VAS=visual analogue scale, XO=crossover

Other abbreviations: ER=extended-release, IR=immediate-release

Pharmacokinetics/Pharmacogenomics

Absorption

The time to peak plasma concentration (T_{max}) of Xtampza ER[®] (oxycodone extended-release) is approximately 4.5 hours after administration of the dose under fed conditions. In pharmacokinetic studies using healthy subjects, steady-state levels were achieved within 24 to 36 hours. When given under fed conditions, the elimination half-life of Xtampza ER[®] (oxycodone extended-release) was 5.6 hours.¹

Xtampza ER[®] (oxycodone extended-release) is not bioequivalent to oxycodone extended-release tablets. Xtampza ER[®] (oxycodone extended-release) has a lower peak serum concentration (C_{max}) and extent of absorption (AUC) than oxycodone extended-release tablets when administered in the fasting state. In the fed state, C_{max} is still lower for Xtampza ER[®] (oxycodone extended-release) than oxycodone extended-release tablets, but the AUC is similar.¹

Distribution

The steady-state volume of distribution (V_{SS}) for oxycodone given intravenous was 2.6 L/kg. Plasma protein binding is approximately 45%. Tissue distribution of oxycodone includes the skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has also been found in breast milk.¹

Metabolism

Oxycodone is extensively metabolized to produce noroxycodone, noroxymorphone and oxymorphone, which are all glucuronidated. The major metabolites are noroxycodone and noroxymorphone. The primary pathway of metabolism is CYP3A mediated N-demethylation to noroxycodone, which undergoes further oxidation to noroxymorphone. Oxymorphone is produced via O-demethylation of oxycodone via CYP2D6; however, this is a minor pathway of metabolism of oxycodone. Noroxycodone, noroxymorphone and oxymorphone are all considered active metabolites; however, their contribution to the analgesia following oxycodone administration is thought to be clinically insignificant.¹

Excretion

The primary pathway for excretion of oxycodone and its metabolites is via the kidney. The total plasma clearance in adults was 84 L/hr. Amounts of oxycodone and its metabolites have been measured in the urine as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free and conjugated noroxymorphone 14%, free oxymorphone < 1%, conjugated oxymorphone 10% and other reduced free and conjugated metabolites up to 18%.¹

Food Effects

Xtampza ER[®] (oxycodone extended-release) is more bioavailable when taken with food, and is dependent upon the food consumed. The oral bioavailability is highest following a high-fat, high-calorie meal, resulting in an increase in C_{max} of 100 to 150% and an increase in AUC of 50 to 60% compared to fasted administration. A medium-fat, medium-calorie meal increased C_{max} by 84% and AUC by 28% compared to fasted administration, and a low-fat, low-calorie meal increased C_{max} by 19% compared to fasted administration. The low-fat, low-calorie meal produced a comparable AUC relative to administration of Xtampza ER[®] (oxycodone extended-release) under fasted conditions. Xtampza ER[®] (oxycodone extended-release) capsules may be opened, and the microspheres may be sprinkled onto soft food for administration without altering pharmacokinetic parameters.¹

Effects of Tampering

Pharmacokinetic studies demonstrated that manipulated Xtampza ER[®] (oxycodone extended-release) was bioequivalent to intact Xtampza ER[®] (oxycodone extended-release) when administered orally.^{1,2}

Pharmacogenomic Considerations:

Overall, numerous genes involved with the pharmacokinetics and dynamics of opioids response are candidate genes in the context of opioid analgesia. The clinical relevance of *CYP2D6* genotyping to predict analgesic outcomes is still relatively unknown; the two extremes in *CYP2D6* genotype (ultrapid

and poor metabolism) seem to predict pain response and/or adverse effects. Overall, the level of evidence linking genetic variability (*CYP2D6* and *CYP3A4*) to oxycodone response and phenotype (altered biotransformation of oxycodone into oxymorphone and overall clearance of oxycodone and oxymorphone) is strong; however, there has been no randomized clinical trial on the benefits of genetic testing prior to oxycodone therapy.¹⁰

Table 3. Pharmacokinetics¹

Generic Name	T _{max} (hours)	Duration (hours)	Renal Clearance (L/h)	Active Metabolites	Serum Half-Life (hours)
Oxycodone	4.5	12	84	Noroxycodone, noroxymorphone and oxymorphone	5.6

Special Populations**Table 4. Special Populations¹**

Population	Precaution
Elderly	Pharmacokinetic studies have demonstrated that clearance of oxycodone is slightly reduced in subjects over the age of 65. Plasma concentrations of oxycodone were increased by approximately 15%. The phase III trial for Xtampza ER [®] (oxycodone extended-release) included 88 subjects, and no untoward or unexpected adverse reactions were seen in this subgroup of the study population. Usual doses and dosing intervals may be appropriate for elderly patients. Caution is recommended for elderly patients, and doses may be started at the low end of the dosing range.
Renal Dysfunction	Plasma concentrations of oxycodone are approximately 50% higher in patients with renal impairment (< 60 mL/min) compared to patients with normal renal function. A conservative approach to dose initiation and adjustment is recommended. Use of alternative analgesics is recommended for patients that require doses of Xtampza ER [®] (oxycodone extended-release) less than 9 mg.
Hepatic Dysfunction	Patients with hepatic impairment demonstrated greater plasma concentrations of oxycodone than patients with normal hepatic function with equivalent doses. It is recommended to start patients with hepatic impairment at 1/3 to 1/2 the usual starting dose, followed by careful dose titration.
Pregnancy/Lactation	Prolonged use of opioids during pregnancy may cause neonatal withdrawal syndrome. Data is not available regarding a drug-associated risk of birth defects or miscarriage with Xtampza ER [®]

Population	Precaution
	<p>(oxycodone extended-release). In animal studies during the period of organogenesis, there was no embryo-fetal toxicity at doses equivalent to 0.5 to 15 times the adult human dose of 160 mg/day. In animal studies during the perinatal period, there was transiently decreased pup bodyweight during lactation and the early post-weaning period at doses equivalent to approximately 40% of an adult dose of 160 mg/day. Treatment of pregnant rats with oxycodone at both clinically relevant doses and below resulted in neurobehavioral effects in offspring. Based upon animal data, pregnant women should be advised of potential risks to a fetus.</p> <p>Oxycodone is present in breast milk. Concentrations have varied over multiple studies of oxycodone immediate-release. No studies were performed with Xtampza ER[®] (oxycodone extended-release), specifically. Breastfeeding is not recommended during treatment with Xtampza ER[®] (oxycodone extended-release) due to the potential for serious adverse events including excess sedation and respiratory depression.</p>
Children	<p>Safety and effectiveness of Xtampza ER[®] (oxycodone extended-release) have not been established in patients below the age of 18 years.</p>
Gender/Race	<p>Pharmacokinetic studies with Xtampza ER[®] (oxycodone extended-release) indicated that healthy female subjects demonstrate up to 20% higher oxycodone plasma levels than males. This may not be clinically significant, as Xtampza ER[®] (oxycodone extended-release) is intended for chronic use with an individualized dosage.</p>

Dosage Forms

Table 5. Availability, Storage and Handling¹

Dosage Form	Strength	Special Handling or Storage
Extended-release capsule	9 mg 13.5 mg 18 mg 27 mg 36 mg	<p>Store at 25°C (77°F); excursions between 15°C to 30°C (59°F to 86°F) permitted.</p> <p>Dispense and store in a tight, light-resistant container with child-resistant closure.</p>

Dosage Range

Table 6. Dosing and Administration¹

Adult Dose	Pediatric Dose	Renal Dose	Hepatic Dose
<p><u>Pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate:</u> Initial (opioid naïve or patients without opioid tolerance): 9 mg every 12 hours with food.</p> <p>Initial (conversion from other opioids): 9 mg every 12 hours with food. For conversion from transdermal fentanyl, approximately 9 mg every 12 hours should initially be substituted for each 25 µg/hr of fentanyl transdermal patch.</p> <p>Maintenance: Titrate dose to efficacy every 1 to 2 days. The total daily oxycodone dose usually can be increased by 25% to 50% of the current dose each time an increase is clinically indicated.</p> <p>Maximum: 144 mg every 12 hours with food (288 mg per day)</p>	<p>Safety and efficacy in pediatric patients have not been established.</p>	<p>No specific recommendations.</p>	<p>Start dosing at 1/3 to 1/2 the usual starting dose.</p>

Precautions

Boxed Warning for Xtampza ER[®] (oxycodone extended-release)¹

WARNING
<p><u>Addiction, Abuse and Misuse</u> Xtampza ER[®] (oxycodone extended-release) exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing and monitor regularly for these behaviors and conditions.</p> <p><u>Life-Threatening Respiratory Depression</u> Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.</p> <p><u>Accidental Ingestion</u> Accidental ingestion of Xtampza ER[®] (oxycodone extended-release), especially by children, can result in fatal overdose of oxycodone.</p> <p><u>Neonatal Opioid Withdrawal Syndrome</u> Prolonged maternal use of Xtampza ER[®] (oxycodone extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.</p>

WARNING

CYP3A4 Inhibitors or Inducers

Concomitant use with CYP3A4 inhibitors or discontinuation of CYP3A4 inducers can result in fatal overdose of oxycodone from Xtampza ER® (oxycodone extended-release).

Table 7. Warnings/Precautions¹

Warning/ Precaution	Addiction, Abuse and Misuse; Xtampza ER® (oxycodone extended-release) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Xtampza ER® (oxycodone extended-release), and monitor all patients regularly for the development of these behaviors or conditions.
	Life-Threatening Respiratory Depression; Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER® (oxycodone extended-release). Monitor for respiratory depression, especially during initiation of Xtampza ER® (oxycodone extended-release) or following a dose increase. Accidental ingestion of even one dose of Xtampza ER® (oxycodone extended-release), especially by children, can result in respiratory depression and death due to an overdose of oxycodone.
	Neonatal Opioid Withdrawal Syndrome; Prolonged use of Xtampza ER® (oxycodone extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
	Cytochrome P450 3A4 Inhibitors and Inducers; Concomitant use of Xtampza ER® (oxycodone extended-release) with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungals (e.g., ketoconazole) and protease inhibitors (e.g., ritonavir), may increase oxycodone plasma concentrations and prolong opioid adverse reactions, which may lead to potentially fatal respiratory depression. This is of particular importance when an inhibitor is added to a stable dose of Xtampza ER® (oxycodone extended-release). Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, or phenytoin, in patients treated with Xtampza ER® (oxycodone extended-release) may increase oxycodone plasma concentrations and prolong opioid adverse reactions. Patients should be monitored closely at frequent intervals when using Xtampza ER® (oxycodone extended-release) with CYP3A4 inhibitors or discontinuing CYP3A4 inducers until stable effects are achieved. Conversely, concomitant use of CYP3A4 inducers or discontinuation of a CYP 3A4 inhibitor could decrease plasma concentrations of oxycodone, leading to decreased opioid efficacy or development of withdrawal syndrome in patients that are physically dependent upon oxycodone. When concomitant use of CYP3A4 inducers or discontinuing a CYP3A4 from a regimen is necessary, patients should be closely monitored at frequent intervals and consideration should be given to increasing the opioid dosage if needed.
	Interactions with Central Nervous System (CNS) Depressants; Hypotension, profound sedation, coma, respiratory depression and death may result if Xtampza ER® (oxycodone extended-release) is used concomitantly with alcohol or other CNS depressants. When considering the use of Xtampza ER® (oxycodone extended-release) in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the tolerance that has developed to the CNS depressant. The patient's use of alcohol or illicit drugs that cause CNS depression should also be evaluated. If Xtampza ER® (oxycodone

	<p>extended-release) is to be used, start with 1/3 to 1/2 the usual starting dose of Xtampza ER[®] (oxycodone extended-release), monitor for signs and symptoms of respiratory depression, sedation and hypotension. Consider using a lower dose of the concomitant CNS depressant.</p>
	<p>Use in Elderly, Cachectic and Debilitated Patients; Life-threatening respiratory depression is more likely to occur in elderly, cachectic or debilitated patients due to potential for altered pharmacokinetics or clearance compared to younger, healthier patients. These patients should be monitored closely, particularly upon initiating and titrating Xtampza ER[®] (oxycodone extended-release) and when other drugs that depress respiration are concomitantly administered. Alternatively, consider the use of non-opioid analgesics in these patients.</p>
	<p>Use in Patients with Chronic Pulmonary Disease; Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients that have a substantially decreased respiratory reserve, hypoxia, hypercapnia or preexisting respiratory depression for respiratory depression, particularly when initiating therapy with Xtampza ER[®] (oxycodone extended-release), as even usual therapeutic doses of Xtampza ER[®] (oxycodone extended-release) may decrease respiratory drive to the point of apnea in these patients.</p>
	<p>Adrenal Insufficiency; Cases of adrenal insufficiency have been reported with opioid use, particularly following greater than one month of opioid therapy. Adrenal insufficiency may present with nonspecific signs and symptoms 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 testing confirms adrenal insufficiency, treat with replacement doses of corticosteroids and taper off of the opioid to allow adrenal function to recover. Other opioids may be tried, as some cases have reported use of a different opioid without recurrence of adrenal insufficiency. No specific opioid has been identified as more likely to cause adrenal insufficiency.</p>
	<p>Hypotensive Effect; Xtampza ER[®] (oxycodone extended-release) may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is additional risk for patients with compromised ability to maintain blood pressure due to depleted blood volume or concomitant administration of certain CNS depressant drugs that compromise vasomotor tone, such as phenothiazines or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Xtampza ER[®] (oxycodone extended-release). The use of Xtampza ER[®] (oxycodone extended-release) should be avoided in patients with circulatory shock, as Xtampza ER[®] (oxycodone extended-release) may cause vasodilation that can further reduce cardiac output and blood pressure.</p>
	<p>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 CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Xtampza ER[®] (oxycodone extended-release) may reduce respiratory drive, leading to CO₂ retention and further increase in intracranial pressure. Monitor patients for signs of sedation and respiratory depression, particularly upon initiation of therapy. Opioid analgesics can also produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. Avoid the use of Xtampza ER[®] (oxycodone extended-release) in patients with impaired consciousness or coma.</p>
	<p>Risks of Use in Patients with Gastrointestinal Conditions; Use of Xtampza ER[®] (oxycodone extended-release) in patients with gastrointestinal obstruction, including paralytic ileus is contraindicated. Oxycodone may cause spasm of the sphincter of Oddi. Opioids may increase serum amylase. Monitor patients with</p>

	biliary tract disease, including acute pancreatitis, for worsening of symptoms.
	Risk of Use in Patients with Seizure Disorders; The oxycodone in Xtampza ER [®] (oxycodone extended-release) may increase the frequency of seizures in patients with seizure disorders and increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during treatment with Xtampza ER [®] (oxycodone extended-release).
	Withdrawal; Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine and buprenorphine) or partial agonists (e.g., buprenorphine) in patients receiving therapy with a full opioid agonist, including Xtampza ER [®] (oxycodone extended-release). Mixed agonist/antagonists may reduce the analgesic effects of full agonist opioids and/or precipitate withdrawal symptoms. When discontinuing Xtampza ER [®] (oxycodone extended-release), gradually taper the dosage. Do not abruptly discontinue Xtampza ER [®] (oxycodone extended-release).
	Driving and Operating Machinery; Xtampza ER [®] (oxycodone extended-release) may impair the mental and physical abilities necessary to perform potentially hazardous activities such as driving a vehicle or operating machinery. Patients should be warned not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER [®] (oxycodone extended-release) and know how they will react to the medication.
	Laboratory monitoring; Not every urine drug test for opioids or opiates detect oxycodone reliably, especially tests designed for in-office use. Some laboratories will report urine drug concentrations below a specified "cut-off" value as negative. If urine testing for oxycodone is considered in a patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

Contraindications

Table 8. Contraindications¹

Contraindication	Xtampza ER [®] (oxycodone extended-release) is contraindicated in patients with severe respiratory depression.
	Xtampza ER [®] (oxycodone extended-release) is contraindicated in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
	Xtampza ER [®] (oxycodone extended-release) is contraindicated in patients with known or suspected paralytic ileus and gastrointestinal obstruction.
	Xtampza ER [®] (oxycodone extended-release) is contraindicated in patients with hypersensitivity to oxycodone

Adverse Effects

Table 10 represents adverse reactions reported in > 5% of subjects from both the open-label titration period and double-blind treatment period of the phase III clinical trial for Xtampza ER[®] (oxycodone extended-release). Figures reported during the open-label titration phase are reported in the active drug column.

Table 9. Adverse Events¹

Adverse Event (%)	Reported Frequency	
	Active Drug, Dosing Regimen N=740 (open-label titration phase), 193 (double-blind treatment phase) (%)	Placebo N=196 (%)
Nausea	16.6, 10.9	4.6

Adverse Event (%)	Reported Frequency	
	Active Drug, Dosing Regimen N=740 (open-label titration phase), 193 (double-blind treatment phase) (%)	Placebo N=196 (%)
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

Drug Interactions

Table 10. Drug Interactions^{1,11}

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
CYP3A4 Inhibitors	Major	CYP3A4 inhibitors may inhibit the metabolism of oxycodone, resulting in increased plasma concentrations of oxycodone and prolonged opioid effects. When concomitant administration of CYP3A4 inhibitors and oxycodone is necessary, patients should be evaluated at frequent intervals and dose adjustments should be considered until stable drug effects are achieved.
Central Nervous System (CNS) Depressants	Major	Concomitant administration of oxycodone with other CNS depressants can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving concomitant CNS depressants for signs of respiratory depression, sedation and hypotension. When using oxycodone and another CNS depressant, consider reducing the dose of one or both agents.
Mixed Agonist/Antagonist and Partial Agonist Opioids	Major	Mixed agonist/antagonist and partial agonist opioid analgesics may reduce the analgesic effect of oxycodone or precipitate withdrawal symptoms. The concomitant use of mixed agonist/antagonist or partial opioid agonist analgesics with oxycodone should be avoided.
Muscle Relaxants	Major	Oxycodone may enhance neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients for signs of respiratory depression and decrease the dosage of oxycodone and/or the muscle relaxant as necessary. Concurrent use of oxycodone and cyclobenzaprine, orphenadrine, carisoprodol or tizanidine may also increase risk of paralytic ileus.
Serotonergic Drugs	Major	Concomitant use of opioids and serotonergic drugs has resulted in serotonin syndrome. If concomitant use is necessary, carefully observe the patient, particularly during treatment initiation and dose adjustments. If serotonin syndrome is suspected, discontinue oxycodone.
CYP2D6 Inhibitors	Moderate	CYP2D6 inhibitors may inhibit the metabolism of oxycodone, resulting in increased plasma concentrations of oxycodone and prolonged opioid effects. When concomitant administration of CYP2D6 inhibitors and oxycodone is necessary, patients should be evaluated at frequent intervals and dose adjustments should be considered until stable drug effects are achieved.

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
CYP3A4 Inducers	Moderate	CYP3A4 inducers may induce the metabolism of oxycodone resulting in increased clearance of oxycodone and lower plasma concentrations of oxycodone. This may result in lack of efficacy or possibly withdrawal syndrome. Monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.
Diuretics	Moderate	Concomitant use of opioids with diuretics can decrease the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of reduced diuresis and/or effects on blood pressure. The dose of the diuretic may be increased as needed.
Kava	Moderate	Concomitant use of opioids with kava may result in increased CNS depression.
Ginseng	Moderate	Concomitant use of opioids with ginseng may result in decreased efficacy of analgesia of opioids.
St. John's Wort	Moderate	Concomitant use of oxycodone and St. John's Wort may result in decreased oxycodone exposure and plasma concentrations.
Valerian	Moderate	Concomitant use of opioids with valerian may result in increased CNS depression.
Anticholinergics	Unknown	Concomitant use of opioids with anticholinergics or other drugs with anticholinergic activity may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation, in addition to respiratory and CNS depression.

*Severity rating per Micromedex

Patient Monitoring Guidelines^{1,11}

Before starting therapy with an opioid, individuals should be evaluated for potential signs of addiction, abuse or misuse of medications. If started, they should continue to be monitored frequently for any changes in behavior. While the individual is receiving opioid analgesics they should be monitored for adequacy of analgesia as well as continually assessed for the need of continued opioid treatment.

The following signs and symptoms should be monitored during therapy with opioids:

- respiratory depression and sedation; especially within 24 to 72 hours following treatment initiation and after dose increases; and particularly in high risk patient (elderly, cachectic, and debilitated patients and those with preexisting respiratory depression or otherwise significantly reduced respiratory reserve)
- exacerbation of biliary tract disease
- hypotension; in ambulatory patients; on initiation and with dose titration; especially when ability to maintain blood pressure is compromised
- worsened seizure control; in patients with a history of seizure disorders

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