
Drug Monograph

Generic Name: oxycodone/naltrexone extended-release

Trade Name: Troxyca[®] ER

Dosage Form: Extended-release capsule

NDCs: 60793-537-01, 60793-531-01, 60793-535-01, 60793-532-01, 60793-533-01, 60793-536-01

Manufacturer: Pfizer Inc.

ADF Product Classification: Agonist/Antagonist combination

Executive Summary

Troxyca[®] ER (oxycodone/naltrexone extended-release) is a combination of oxycodone hydrochloride, an opioid agonist, and naltrexone hydrochloride, an opioid antagonist, and is Food and Drug Administration (FDA)-approved for the management of pain that is 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. It is not indicated for use on an as-needed basis.¹ Troxyca[®] ER (oxycodone/naltrexone 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.

The efficacy and safety of Troxyca[®] ER (oxycodone/naltrexone extended-release) was evaluated in two phase III clinical trials.²⁻⁴ The first trial was a multicenter, enriched-enrollment, randomized, double-blind, placebo-controlled study in adults who had experienced at least three months of moderate-to-severe nonspecific chronic lower back pain (CLBP) not caused by another condition (N=410). Following a titration phase, 281 patients were randomized to receive either Troxyca[®] ER (oxycodone/naltrexone extended-release) or placebo for 12 weeks. In the final two weeks of the double-blind treatment period, treatment with Troxyca[®] ER (oxycodone/naltrexone extended-release) was associated with a lower increase in mean numeric rating scale (NRS) pain score from baseline (0.60; 95% confidence interval [CI], 0.27 to 0.93) compared to placebo (1.23; 95% CI, 0.87 to 1.58; difference, -0.62; P=0.0114). Notably, treatment with Troxyca[®] ER (oxycodone/naltrexone extended-release) and placebo were both associated with an overall increase in mean NRS pain score from baseline in the final two weeks of the 12-week double-blind treatment period.³ The second trial was a multicenter, open-label study in adults with moderate-to-severe chronic non-cancer pain (CNCP) (N=395). The primary endpoint was the number and type of treatment-emergent adverse events (TEAE) associated with treatment with Troxyca[®] ER (oxycodone/naltrexone extended-release) for up to 12 months; a total of 343 patients (86.8%) reported TEAE, but only 207 patients (52.4%) reported treatment-related adverse events. Treatment with Troxyca[®] ER (oxycodone/naltrexone extended-release) was associated with a statistically significant decrease from baseline in mean Brief Pain Inventory (BPI) scores for worst, least, and average pain over the previous 24 hours and current pain at all visits except for least pain and current pain at week one (P≤0.0273).^{2,4}

Troxyca[®] ER (oxycodone/naltrexone extended-release) is formulated as a capsule that contains pellets consisting of oxycodone hydrochloride and sequestered naltrexone hydrochloride. Manipulation of these pellets by crushing, dissolving, or chewing could lead to a rapid release and absorption of a potentially fatal dose of oxycodone, as well as a sufficient quantity of naltrexone to precipitate withdrawal in opioid-dependent individuals.¹ Troxyca[®] ER (oxycodone/naltrexone extended-release) is the only ADF of oxycodone that has FDA-approved abuse-reduction claims in the labeling for both oral and intranasal routes of abuse.² Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules utilize a mechanism of abuse-deterrence similar to that of Embeda[®] (morphine sulfate/naltrexone extended-release) capsules; both capsules contain pellets composed of an opioid agonist with an opioid antagonist sequestered in the core of each pellet.⁵

In addition to *in vitro* manipulation and extraction studies, Troxyca[®] ER (oxycodone/naltrexone 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, drug high, and willingness to take drug again scores for both crushed and intact Troxyca[®] ER (oxycodone/naltrexone extended-release) were significantly lower than for crushed oxycodone immediate-release (IR).⁶ In the intranasal clinical abuse potential study, drug liking, drug high, and willingness to take drug again scores for crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) were significantly lower than for crushed oxycodone IR.⁷ In a simulated intravenous abuse potential study, drug liking scores and scores for feeling high on the drug for simulated crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) were significantly lower than for intravenous oxycodone. However, it is unknown whether the results of the study simulating intravenous abuse potential truly predict a reduction in abuse by the intravenous route. As it becomes available, postmarketing data may provide more information on the abuse liability of Troxyca[®] ER (oxycodone/naltrexone extended-release).^{2,8}

Reference Data

Troxyca[®] ER (oxycodone/naltrexone extended-release) is a combination of oxycodone hydrochloride, an opioid agonist, and naltrexone hydrochloride, an opioid antagonist, and is FDA-approved for the management of pain that is 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. It is not indicated for use on an as-needed basis. The FDA has designated this drug a schedule II controlled substance due to the associated risks of addiction, abuse, and misuse, even at recommended treatment doses. Similarly to other extended-release opioid analgesics, it is also associated with greater risks of overdose and death.¹

Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules contains pellets consisting of oxycodone hydrochloride and sequestered naltrexone hydrochloride at a ratio of 100:12. Oxycodone is a full opioid agonist and is relatively selective for the μ -opioid receptor; although, it can bind to other opioid receptors at higher doses. The primary therapeutic action of oxycodone is analgesia; however, it may also result in respiratory depression, reduced gastrointestinal motility, and changes in the circulatory, endocrine, and autonomic nervous systems. Naltrexone is a centrally-acting, μ -opioid antagonist that reverses the subjective and analgesic effects of μ -opioid agonists by competitively binding at the μ -opioid receptors. When Troxyca[®] ER (oxycodone/naltrexone extended-release) is taken orally as directed, the oxycodone relieves pain while the sequestered naltrexone passes through the body with no clinical effect. However, if Troxyca[®] ER (oxycodone/naltrexone extended-release) is crushed, chewed, or dissolved, up to 100% of the sequestered naltrexone is released, reversing the effects of oxycodone and potentially precipitating withdrawal in opioid-tolerant individuals. Due to the presence of talc as one of the product excipients, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.¹

Troxyca[®] ER (oxycodone/naltrexone extended-release) is the only ADF of oxycodone that has FDA-approved abuse-reduction claims in the labeling for both oral and intranasal routes of abuse.² Troxyca[®] ER (oxycodone/naltrexone extended-release) is only the second oral agent in an extended-release capsule formulation to utilize a sequestered core of the μ -opioid antagonist, naltrexone; the first to utilize this mechanism of abuse deterrence was Embeda[®] (morphine sulfate-naltrexone extended-release).⁴ Other oxycodone formulations with FDA-approved labeling describing abuse-deterrent properties include OxyContin[®] (oxycodone extended-release) tablets, Targiniq[®] ER (oxycodone/naloxone extended-release) tablets, and Xtampza[®] ER (oxycodone extended-release) capsules.⁹⁻¹¹ Table 1 outlines the currently available, long-acting opioid therapies and whether they have a designated abuse-deterrent formulation available per package labeling.

Table 1. Long-Acting Opioid Availability¹²⁻¹⁴

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

*Manufacturer reports launch scheduled for Q1 2017

Therapeutic Indications/Efficacy

The available efficacy and safety studies, as well as trials assessing the abuse-deterrence of Troxyca® ER (oxycodone/naltrexone extended-release), are outlined in Table 2.

A multicenter, enriched-enrollment, randomized, double-blind, placebo-controlled, phase III study involving 410 patients with nonspecific CLBP evaluated the efficacy of Troxyca® ER (oxycodone/naltrexone extended-release). Following a titration phase, 281 subjects were randomized to either Troxyca® ER (oxycodone/naltrexone extended-release) or placebo for 12 weeks. In the final two weeks of the double-blind treatment period, treatment with Troxyca® ER (oxycodone/naltrexone extended-release) was associated with a lower increase in mean NRS pain score from baseline (0.60; 95% CI, 0.27 to 0.93) compared to placebo (1.23; 95% CI, 0.87 to 1.58; difference, -0.62; P=0.0114). Treatment with Troxyca® ER (oxycodone/naltrexone extended-release) and placebo were both associated with an overall increase in mean NRS pain score from baseline in the final two weeks of the 12-week double-blind treatment period. Greater proportions of patients treated with Troxyca® ER (oxycodone/naltrexone extended-release) reported a ≥30% decrease (57.5 vs 44.0%, respectively; P=0.0248) and a ≥50% decrease (39.7 vs 29.9%, respectively; P=0.0874) in weekly average NRS pain score from baseline to the final two weeks of treatment compared to placebo. Changes in Roland Morris Disability Questionnaire (RMDQ) score and Patient Global Assessment (PGA) of low back pain from baseline to 12 weeks were not significantly different between treatment groups. Treatment with Troxyca® ER (oxycodone/naltrexone extended-release) was associated with a numerically lower rate of acetaminophen use compared to placebo (34.9 vs 43.3%), as well as a lower average dose (167.7 vs 252.1 mg/day, respectively; P=0.939). A total of 27.2% of patients randomized to treatment with Troxyca® ER (oxycodone/naltrexone extended-release) discontinued treatment during the double-blind treatment

period. Notably, only 43.6% of patients in the intent-to-treat population had used opioids in the 30 days prior to the initiation of the study.³

A multicenter, open-label, phase III study involving 395 patients with moderate-to-severe CNCP evaluated the safety and efficacy of Troxycan[®] ER (oxycodone/naltrexone extended-release) over 12 months. Opioid-naïve patients initiated therapy with Troxycan[®] ER (oxycodone/naltrexone extended-release) 10 mg twice daily and opioid-experienced patients converted to Troxycan[®] ER (oxycodone/naltrexone extended-release) based on their current daily opioid dose; dose adjustments were made at the investigator's discretion. The primary endpoint was the number and type of TEAE associated with treatment with Troxycan[®] ER (oxycodone/naltrexone extended-release) for up to 12 months. A total of 343 patients (86.8%) reported TEAE. However, only 207 patients (52.4%) reported treatment-related adverse events. The most common TEAE leading to discontinuation were nausea (4.6%), constipation (2.5%), and vomiting (2.0%). A total of 26 patients (6.6%) reported serious adverse events. The incidence of any TEAE was similar between opioid-naïve (85.9%) and opioid-experienced (87.1%) patients. The decrease from baseline in mean BPI scores for worst, least, and average pain over the previous 24 hours and current pain was statistically significant at all visits except for least and current pain at week one ($P \leq 0.0273$). A total of 158 patients (40.0%) completed the 12 months of treatment. The most common reasons for discontinuation included TEAE (19.0%), withdrawal of consent (12.9%), and lack of efficacy (9.4%).^{2,4}

Troxycan[®] ER (oxycodone/naltrexone extended-release) has been evaluated in abuse deterrence studies.^{6,7} In a single-center, randomized, double-blind, double-dummy, placebo-controlled, phase I, six-way crossover study that compared orally-administered crushed Troxycan[®] ER (oxycodone/naltrexone extended-release) and intact Troxycan[®] ER (oxycodone/naltrexone extended-release) capsules to crushed oxycodone IR tablets and placebo in nondependent recreational opioid users, the mean peak effects of treatment based on the visual analogue scale (VAS) for "drug liking" were 70.2, 59.3, 74.5, 85.5, 89.8, and 51.6 for the crushed 40 mg/4.8 mg pellets, intact 60 mg/7.2 mg capsules, crushed 60 mg/7.2 mg pellets, crushed oxycodone IR 40 mg tablets, crushed oxycodone IR 60 mg tablets, and placebo, respectively ($P \leq 0.0001$ for drug vs oxycodone IR; $P \leq 0.05$ for drug vs placebo). The mean peak effects of treatment on the VAS for "high" were 55.4, 9.7, 71.6, 112.1, 117.7, and 2.8 for the crushed 40 mg/4.8 mg pellets, intact 60 mg/7.2 mg capsules, crushed 60 mg/7.2 mg pellets, crushed oxycodone IR 40 mg tablets, crushed oxycodone IR 60 mg tablets, and placebo, respectively ($P \leq 0.0001$ for drug vs oxycodone IR; $P \leq 0.05$ for drug vs placebo). Mean "take drug again" scores based on the VAS were also significantly lower for all dosages of crushed and intact Troxycan[®] ER (oxycodone/naltrexone extended-release) compared to corresponding doses of crushed oxycodone IR ($P < 0.001$), with the exception of crushed Troxycan[®] ER (oxycodone/naltrexone extended-release) 60 mg/7.2 mg vs crushed oxycodone IR 60 mg. All crushed doses were administered as oral solutions.⁶

In a randomized, double-blind, placebo and active-controlled, phase I, four-way crossover study that compared intranasally-administered crushed Troxycan[®] ER (oxycodone/naltrexone extended-release) to crushed oxycodone IR tablets and placebo in nondependent recreational opioid users, the mean peak effects of treatment based on the VAS for "drug liking" were 51.0, 60.5, 51.3, and 92.8 for the Troxycan[®] ER placebo, crushed 30 mg/3.6 mg pellets, the oxycodone IR placebo, and crushed oxycodone IR 30 mg tablets, respectively ($P \leq 0.01$ for drug vs placebo; $P \leq 0.0001$ for drug vs oxycodone IR). The mean peak effects of treatment on the VAS for "high" were 0.7, 25.2, 7.0, and 86.9 for the Troxycan[®] ER placebo, crushed 30 mg/3.6 mg pellets, the oxycodone IR placebo, and crushed oxycodone IR 30 mg tablets, respectively ($P \leq 0.01$ for drug vs placebo; $P \leq 0.0001$ for drug vs oxycodone IR). Mean "take drug again" scores based on the VAS were also significantly lower for crushed Troxycan[®] ER (oxycodone/naltrexone extended-release) compared to the corresponding dose of crushed oxycodone IR ($P \leq 0.0001$).⁷

A single-center, randomized, double-blind, placebo-controlled, phase I, three-way crossover study aimed to simulate the effects of injection of crushed Troxycan[®] ER (oxycodone/naltrexone extended-release) by comparing intravenous administration of a single dose of crushed oxycodone 20 mg and naltrexone 2.4 mg in solution to single doses of oxycodone 20 mg or placebo (0.9% sodium chloride) in

nondependent recreational opioid users. The mean peak effects of treatment based on the VAS for “drug liking” were 58.2, 92.4, and 52.2 for simulated crushed Troxyca[®] ER (oxycodone/naltrexone extended-release), oxycodone, and placebo, respectively ($P \leq 0.0001$ for drug vs placebo; $P \leq 0.001$ for drug vs oxycodone). The mean peak effects of treatment based on the VAS for “high” were 17.2, 93.1, and 3.4 for simulated crushed Troxyca[®] ER (oxycodone/naltrexone extended-release), oxycodone, and placebo, respectively ($P \leq 0.0001$ for drug vs placebo; $P \leq 0.001$ for drug vs oxycodone). Mean “take drug again” scores based on the VAS were also significantly lower for simulated crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) compared to the corresponding dose of oxycodone ($P \leq 0.001$).^{2,8}

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Rauck et al^{3*}</p> <p>Oxycodone/naltrexone ER capsules 20 mg to 160 mg oxycodone component</p> <p>vs</p> <p>placebo</p> <p>All patients were titrated to an individualized total daily dose of oxycodone/naltrexone ER capsules between 20 mg and 160 mg of oxycodone during a four-to-six week OL titration phase.</p> <p>At randomization, patients were randomized to continue their dose or a blinded two week taper to placebo for the 12 week DB treatment phase.</p> <p>Patients who completed the 12 week DB treatment phase or discontinued before the end of 12 weeks entered a two week post-treatment phase, during which they were tapered off of</p>	<p>MC, DB, PC, RCT</p> <p>Patients aged 18 years or older with nonspecific moderate-to-severe CLBP for at least three months prior to screening and without active major depression in the past year, BMI >40 kg/m², positive urine toxicology test for illicit substances, history of drug or alcohol abuse, or co-morbid pain conditions within the past two years that could interfere with the assessment of self-evaluation of CLBP</p>	<p>N=410</p> <p>12 weeks</p>	<p>Primary:</p> <p>Mean change in weekly average NRS pain score from randomization to the final two weeks of the DB treatment phase</p> <p>Secondary:</p> <p>Change in mean RMDQ total score and proportion of patients with each PGA category for low back pain from randomization to week 12, 5-point categorical Satisfaction with Treatment, BPI-sf, and use of rescue acetaminophen, safety and tolerability, signs and symptoms of opiate withdrawal via COWS</p>	<p>Primary:</p> <p>Treatment with oxycodone/naltrexone ER was associated with a lower increase in mean NRS pain score (0.60; 95% CI, 0.27 to 0.93) compared to placebo (1.23; 95% CI, 0.87 to 1.58; difference, -0.62; P=0.0114). The mean (SD) weekly NRS pain score at baseline was 3.0 (1.25) for the oxycodone/naltrexone ER group and 3.1 (1.04) for the placebo group. During the final two weeks of the treatment period, these scores increased to 3.6 (2.04) and 4.3 (2.24) for oxycodone/naltrexone ER and placebo, respectively.</p> <p>Secondary:</p> <p>Changes in mean RMDQ score from randomization to 12 weeks were not significantly different between oxycodone/naltrexone ER and placebo (0.67 vs 0.50; P=0.7547).</p> <p>Changes in proportions of patients with each PGA category of low back pain from randomization to 12 weeks were not significantly different between oxycodone/naltrexone ER and placebo (P=0.1272).</p> <p>Greater proportions of patients treated with oxycodone/naltrexone ER reported a ≥30% decrease (57.5 vs 44.0%, respectively; P=0.0248) and a ≥50% decrease (39.7 vs 29.9%, respectively; P=0.0874) in weekly average NRS pain score from randomization to the final two weeks of treatment compared to placebo.</p> <p>The time to loss of 30% and 50% analgesic response was statistically significantly longer with oxycodone/naltrexone ER than with placebo (P = 0.0024 for 30% and P = 0.0021 for 50%). Patients treated with oxycodone/naltrexone ER took a significantly longer time to discontinue treatment due to investigator-reported lack of efficacy during the double-blind</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxycodone/naltrexone ER or placebo.				<p>treatment period when compared with patients receiving placebo (P = 0.006).</p> <p>Treatment with oxycodone/naltrexone ER was associated with a numerically lower rate of acetaminophen use compared to placebo (34.9 vs 43.3%), as well as a lower average dose (167.7 vs 252.1 mg/day, respectively; P=0.939).</p> <p>A significantly greater proportion of patients treated with oxycodone/naltrexone ER reported being satisfied or very satisfied with treatment compared to placebo (79.7 vs 59.2%, respectively; P=0.0004).</p> <p>Significant differences were observed between oxycodone/naltrexone ER and placebo for all subscales of the BPI-sf from randomization to weeks 8 and 12, with the exception of worst pain and pain interference index at week 8. Average pain scores were lower with oxycodone/naltrexone ER (3.1 at week 8, 3.2 at week 12) compared to placebo (3.9 at week 8, 4.2 at week 12). Mean changes for the BPI-sf subscales for worst pain (0.4 vs 1.4, respectively; P<0.0001) and pain interference (0.4 vs 1.1, respectively; P=0.0018) were lower with oxycodone/naltrexone ER compared to placebo.</p> <p>A total of 12 patients (8.2%) in the oxycodone/naltrexone ER group and eight patients (6.0%) in the placebo group discontinued treatment during the double-blind treatment period because of TEAE. A total of 83 patients (56.8%) in the oxycodone/naltrexone ER group and 75 patients (56.0%) in the placebo group experienced at least one TEAE; a total of 39 patients (26.7%) in the oxycodone/naltrexone ER group and 23 patients (17.2%) in the placebo group experienced at least one treatment-related TEAE.</p> <p>During the DB treatment phase, 95% of patients in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>oxycodone/naltrexone ER group and 97.6% of patients in the placebo group had maximum COWS scores <5, which indicates no opiate withdrawal. A total of seven patients (5%) in the oxycodone/naltrexone ER group and two patients (1.6%) in the placebo group had maximum COWS scores between 5 and 12, which indicates mild withdrawal. One patient (0.8%) in the placebo group had a maximum COWS score between 13 and 24, which indicates moderate withdrawal.</p> <p>No significant changes in vital signs, 12-lead ECG, or laboratory values were observed during the study.</p> <p>Patients treated with oxycodone/naltrexone ER had mean oxycodone plasma concentrations of 25.9 ng/mL and 22.6 ng/mL at randomization and week 12, respectively. Mean noroxycodone plasma concentrations were 27.1 ng/mL at randomization and 26.3 ng/mL at week 12. Plasma oxycodone and noroxycodone concentrations increased in a dose-related manner and were relatively constant between week four and the end of the study.</p> <p>The naltrexone plasma concentrations in patients treated with oxycodone/naltrexone ER were below the limit of quantification (<4 pg/mL) in 82% of samples collected across study visits. In the remaining 18% of samples, a majority 83% were ≤40 pg/mL. Similarly, for 6-β-naltrexol, a majority of observed plasma concentrations were low. The mean (highest) concentration of naltrexone was 5.3 (118) pg/mL at randomization and 3.0 (103) pg/mL at week 12 in patients treated with oxycodone/naltrexone ER. For patients randomized to placebo, the mean (highest) concentration of naltrexone was 24.9 (1090) pg/mL at randomization and 0 pg/mL at week 12.</p> <p>Five patients had naltrexone concentrations >200 pg/mL; none of these patients had adverse events of withdrawal or clinically meaningful COWS scores. In the two patients with the highest</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				observed naltrexone concentrations (581 pg/mL and 1090 pg/mL), COWS scores were ≤ 2 at all visits. Withdrawal syndrome could not be attributed to naltrexone concentrations in any of the four patients treated with oxycodone/naltrexone ER who reported the adverse event of withdrawal syndrome. There was no apparent correlation between plasma naltrexone concentrations and the daily dose of naltrexone present in oxycodone/naltrexone ER. Naltrexone concentrations appeared not to be correlated with pain scores or COWS scores.
<p>Arora et al^{2,4*}</p> <p>Oxycodone/naltrexone ER capsules 3 mg to 189 mg oxycodone component</p> <p>Opioid-naïve patients initiated therapy with oxycodone/naltrexone ER 10 mg BID and opioid-experienced patients converted to oxycodone/naltrexone ER based on their current daily opioid dose; dose adjustments were made at the investigator's discretion.</p>	<p>MC, OL</p> <p>Patients aged 18 years or older with moderate-to-severe CNCP requiring around-the-clock analgesia and not expected to last less than three months, and without documented alcohol or drug abuse within one year of study enrollment or clinically significant medical conditions that would interfere with the study or pose a risk to the patient</p>	<p>N=395</p> <p>12 months</p>	<p>Primary: Number and type of adverse events and treatment-related adverse events</p> <p>Secondary: Changes in laboratory values, vital signs, and 12-lead ECG, opioid withdrawal symptoms assessed via COWS, dosing patterns, aberrant medication-related behaviors assessed via COMMTM, change in BPI score</p>	<p>Primary: A total of 343 patients (86.8%) reported TEAE; only 207 patients (52.4%) reported treatment-related adverse events. The most common TEAE leading to discontinuation were nausea (4.6%), constipation (2.5%), and vomiting (2.0%). The incidence of any TEAE was similar between opioid-naïve (85.9%) and opioid-experienced (87.1%) patients.</p> <p>A total of 26 patients (6.6%) reported serious adverse events. The most common serious adverse events were acute myocardial infarction, non-cardiac chest pain, pneumonia, convulsion, and nephrolithiasis; each was reported by two patients (0.5%). Two patients reported serious adverse events deemed reasonably attributable to the study drug: abdominal pain caused by possible bacterial infection, and cholelithiasis.</p> <p>Secondary: There were no clinically relevant changes in any laboratory values, vital signs, or 12-lead ECG throughout the study.</p> <p>A total of 86.6% of patients had a maximum observed COWS score of 0 to 4, which indicates no opiate withdrawal. COWS scores of 5 to 12, which indicate mild withdrawal, were observed in 13.2% of patients. Moderately severe withdrawal symptoms were reported for one opioid-experienced patient, who was also determined to be non-adherent to the medication based on</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>plasma naltrexone and oxycodone levels below the limits of quantitation.</p> <p>The percentage of patients with COMM™ scores ≥ 9, which indicates aberrant behavior, decreased from 21.3% at baseline to 3.7% at month 11; there was no strong relation observed between COMM™ score and reason for discontinuation.</p> <p>The decrease from baseline in mean pain scores for worst, least, and average pain over the previous 24 hours and current pain was statistically significant at all visits except for least and current pain at week one ($P \leq 0.0273$).</p> <p>Mean steady-state plasma oxycodone levels ranged from 15.1 ng/mL in the 10 to 40 mg dose group to 82.8 ng/mL in the >120 mg dose group. Mean steady-state plasma naltrexone levels ranged from 1.7 pg/mL in the 10 to 40 mg dose group to 11.6 pg/mL in the >120 mg dose group. During the study, neither naltrexone nor 6-β-naltrexol plasma concentrations accumulated.</p>
<p>Setnik et al^{6*}</p> <p>Intact oxycodone/naltrexone ER 60 mg/7.2 mg</p> <p>vs</p> <p>crushed oxycodone/naltrexone ER 60 mg/7.2 mg</p> <p>vs</p> <p>crushed oxycodone/naltrexone ER</p>	<p>AC, DB, DD, PC, RCT, XO</p> <p>Healthy non-dependent recreational opioid users aged 18 to 55 years who have used opioids for non-therapeutic purposes at least 10 times in the past year and at least once in the past eight weeks</p>	<p>N=32</p> <p>Six treatment phases</p>	<p>Primary: LS mean E_{max} and AUE_{0-2h} for “drug liking” and “high” via the VAS</p> <p>Secondary: VAS measures for “take drug again,” “overall drug liking,” “good drug effects,” “bad drug effects,” “any drug</p>	<p>Primary: LS mean E_{max} (95% CI) for “drug liking” via the VAS were 70.2 (64.6 to 75.7), 59.3 (53.7 to 64.9), 74.5 (68.9 to 80.1), 85.5 (79.9 to 91.1), 89.8 (84.2 to 95.4), and 51.6 (46.0 to 57.2) for crushed oxycodone/naltrexone ER 40 mg/4.8 mg, intact oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone IR 40 mg, crushed oxycodone IR 60 mg, and placebo, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.05$ for all comparisons to placebo).</p> <p>LS mean AUE_{0-2h} (95% CI) for “drug liking” via the VAS were 118.4 (109.6 to 127.1), 100.1 (91.4 to 108.9), 127.3 (118.5 to 136.0), 141.3 (132.5 to 150.1), 149.5 (140.7 to 158.3), and 100.1 (91.4 to 108.9) for crushed oxycodone/naltrexone ER 40 mg/4.8 mg, intact oxycodone/naltrexone ER 60 mg/7.2 mg, crushed</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>40 mg/4.8 mg</p> <p>vs</p> <p>crushed oxycodone IR 60 mg</p> <p>vs</p> <p>crushed oxycodone IR 40 mg</p> <p>vs</p> <p>placebo</p> <p>This trial consisted of a screening visit and three phases: a naloxone challenge, a drug discrimination phase, and a treatment phase. The treatment phase consisted of six single-dose phases separated by a washout period of ≥ 5 days.</p> <p>All crushed doses administered during the treatment phase were administered orally as a solution.</p>			<p>effects," "feel sick," "nausea," "sleepy," and "dizzy," pupillometry, safety, plasma oxycodone and naltrexone C_{max}, T_{max}, AUC_{0-2h}, AUC_{inf}, and half-life</p>	<p>oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone IR 40 mg, crushed oxycodone IR 60 mg, and placebo, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.05$ for all comparisons to placebo, except intact oxycodone/naltrexone ER).</p> <p>The majority of patients had a reduction in E_{max} for "drug liking" with crushed oxycodone/naltrexone ER 40 mg/4.8 mg (72%), crushed oxycodone/naltrexone ER 60 mg/7.2 mg (75%), and intact oxycodone/naltrexone ER 60 mg/7.2 mg (91%) relative to their respective doses of crushed oxycodone IR 40 mg and 60 mg.</p> <p>LS mean E_{max} (95% CI) for "high" via the VAS were 46.5 (35.6 to 57.4), 22.5 (11.6 to 33.4), 52.8 (41.9 to 63.7), 78.6 (67.7 to 89.5), 85.7 (74.8 to 96.6), and 10.2 (-0.7 to 21.1) for crushed oxycodone/naltrexone ER 40 mg/4.8 mg, intact oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone IR 40 mg, crushed oxycodone IR 60 mg, and placebo, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.05$ for all comparisons to placebo).</p> <p>LS mean AUE_{0-2h} (95% CI) for "high" via the VAS were 55.4 (40.4 to 70.4), 9.7 (-5.3 to 24.7), 71.6 (56.6 to 86.6), 112.1 (97.1 to 127.1), 117.7 (102.7 to 132.7), and 2.8 (-12.2 to 17.8) for crushed oxycodone/naltrexone ER 40 mg/4.8 mg, intact oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone/naltrexone ER 60 mg/7.2 mg, crushed oxycodone IR 40 mg, crushed oxycodone IR 60 mg, and placebo, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.05$ for all comparisons to placebo, except intact oxycodone/naltrexone ER).</p> <p>The majority of patients had a reduction in E_{max} for "high" with</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>crushed oxycodone/naltrexone ER 40 mg/4.8 mg (78%), crushed oxycodone/naltrexone ER 60 mg/7.2 mg (78%), and intact oxycodone/naltrexone ER 60 mg/7.2 mg (97%) relative to their respective doses of crushed oxycodone IR 40 mg and 60 mg.</p> <p>Secondary: Secondary VAS measures were generally lower for intact or crushed oxycodone/naltrexone ER compared to oxycodone IR. LS mean E_{\max} scores for “overall drug liking” and “take drug again” via the VAS were significantly lower for crushed and intact oxycodone/naltrexone ER and placebo compared to corresponding doses of crushed oxycodone IR ($P < 0.001$), with the exception of crushed oxycodone/naltrexone ER 60 mg/7.2 mg compared to crushed oxycodone IR 60 mg. LS mean E_{\max} scores for “good drug effects” and “any drug effects” via the VAS were significantly lower for crushed and intact oxycodone/naltrexone ER compared to corresponding doses of oxycodone IR ($P < 0.0001$). This difference did not reach statistical significance for crushed oxycodone/naltrexone ER 60 mg/7.2 mg compared to crushed oxycodone IR 60 mg. For “bad drug effects,” “nausea,” and “feel sick,” the majority of the comparisons resulted in significantly higher E_{\max} scores for crushed oxycodone IR compared to placebo; crushed oxycodone/naltrexone ER 60 mg/7.2 mg had significantly lower E_{\max} scores than crushed oxycodone IR 60 mg ($P < 0.05$).</p> <p>Greater decreases in pupil diameter were seen with oxycodone IR compared to corresponding doses of crushed oxycodone/naltrexone ER, and all crushed treatments showed peak effects within one hour post-dose.</p> <p>No deaths or serious adverse events occurred during the treatment phase. Fewer subjects reported adverse events from all causalities after intact or crushed oxycodone/naltrexone ER compared to oxycodone IR, with the exception of “feeling hot”</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>and headache.</p> <p>During the first two hours after each dose, plasma concentrations of oxycodone were lower for intact oxycodone/naltrexone ER compared to crushed oxycodone/naltrexone ER or oxycodone IR. Oxycodone plasma exposures were comparable between crushed oxycodone/naltrexone ER and corresponding dosages of crushed oxycodone IR. Oxycodone mean C_{max} for crushed oxycodone/naltrexone ER 60 mg/7.2 mg was similar to that of crushed oxycodone IR, but was approximately four times greater than that of intact oxycodone/naltrexone ER 60 mg/7.2 mg. Intact oxycodone/naltrexone ER had the longest median T_{max} for oxycodone (12.1 hours) compared to crushed treatments.</p> <p>The majority of subjects had no observable plasma exposures to naltrexone, and most concentrations were below the limit of detection. Naltrexone C_{max} for crushed oxycodone/naltrexone ER 40 mg/4.8 mg and 60 mg/7.2 mg was 1.1 ng/mL and 1.8 ng/mL, respectively, and was achieved within a median T_{max} of 0.6 hours post-dose. The mean half-life for naltrexone for crushed oxycodone/naltrexone ER ranged from 5.4 to 5.6 hours.</p>
<p>Setnik et al^{1*}</p> <p>Crushed oxycodone/naltrexone ER 30 mg/3.6 mg intranasally</p> <p>vs</p> <p>crushed oxycodone IR 30 mg intranasally</p> <p>vs</p> <p>crushed weight-matched</p>	<p>AC, DB, DD, PC, RCT, XO</p> <p>Healthy non-dependent recreational opioid users aged 18 to 55 years with a BMI of 17.5 to 30.5 kg/m² and weight ≥50 kg, without a history or current diagnosis of</p>	<p>N=32</p> <p>Four treatment phases</p>	<p>Primary:</p> <p>LS mean E_{max} and AUE_{0-2h} for “drug liking” and “high” via the VAS</p> <p>Secondary:</p> <p>VAS measures for “take drug again,” “overall drug liking,” “good drug effects,” “bad</p>	<p>Primary:</p> <p>LS mean E_{max} (95% CI) for “drug liking” via the VAS were 60.5 (57.2 to 63.8), 51.0 (47.7 to 54.3), 92.8 (89.5 to 96.1), and 51.3 (48.0 to 54.6) for crushed oxycodone/naltrexone ER 30 mg/3.6 mg, placebo for oxycodone/naltrexone, crushed oxycodone IR 30 mg, and placebo for oxycodone IR, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.01$ for all comparisons to placebo).</p> <p>LS mean AUE_{0-2h} (95% CI) for “drug liking” via the VAS were 105.4 (97.9 to 112.8), 98.8 (91.3 to 106.2), 160.0 (152.5 to 167.4), and 100.4 (92.9 to 107.8) for crushed oxycodone/naltrexone ER 30 mg/3.6 mg, placebo for oxycodone/naltrexone, crushed oxycodone IR 30 mg, and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo of oxycodone/naltrexone ER intranasally</p> <p>vs</p> <p>crushed weight-matched placebo of oxycodone IR intranasally</p> <p>This trial consisted of four phases: a screening phase, a naloxone challenge, a drug discrimination phase, and a treatment phase. The treatment phase consisted of four single-dose phases separated by a washout period of ≥ 5 days.</p>	<p>substance abuse or dependence, who are not seeking treatment for substance-related disorders, and who have used opioids for non-therapeutic purposes at least 10 times in the past year and at least once in the past eight weeks, and who have used opioids intranasally at least three times in the past year</p>		<p>drug effects," "any drug effects," "feel sick," "nausea," "sleepy," and "dizzy," pupillometry, safety, plasma oxycodone and naltrexone C_{max}, T_{max}, AUC_{0-2h}, AUC_{inf}, AUC_{last}, and half-life</p>	<p>placebo for oxycodone IR, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.01$ for oxycodone IR vs placebo).</p> <p>LS mean E_{max} (95% CI) for "high" via the VAS were 25.2 (17.6 to 32.9), 0.7 (-7.0 to 8.3), 86.9 (79.3 to 94.6), and 7.0 (-0.7 to 14.6) for crushed oxycodone/naltrexone ER 30 mg/3.6 mg, placebo for oxycodone/naltrexone, crushed oxycodone IR 30 mg, and placebo for oxycodone IR, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.01$ for all comparisons to placebo).</p> <p>LS mean AUE_{0-2h} (95% CI) for "high" via the VAS were 27.1 (15.3 to 38.9), 0.2 (-11.6 to 12.0), 136.4 (124.6 to 148.2), and 5.6 (-6.2 to 17.5) for crushed oxycodone/naltrexone ER 30 mg/3.6 mg, placebo for oxycodone/naltrexone, crushed oxycodone IR 30 mg, and placebo for oxycodone IR, respectively ($P \leq 0.0001$ for all comparisons of oxycodone/naltrexone ER to oxycodone IR; $P \leq 0.01$ for all comparisons to placebo).</p> <p>The "drug liking" and "high" effects of crushed oxycodone IR rose rapidly and peaked at 30 minutes post-dose, followed by a steep decline within three to 4 hours and a gradual decline by 12 to 24 hours toward placebo levels. The peak effects of crushed oxycodone/naltrexone ER occurred at 15 to 30 minutes post-dose, but both "drug liking" and "high" were lower across all time points compared to oxycodone IR.</p> <p>The majority of patients (93%) receiving crushed oxycodone/naltrexone ER experienced a reduction in E_{max} for "drug liking" compared to those receiving oxycodone IR. Reductions of $\geq 30\%$ and $\geq 50\%$ in "drug liking" relative to oxycodone IR were experienced by 89% and 82% of patients, respectively, receiving oxycodone/naltrexone ER. Reductions of $\geq 30\%$ and $\geq 50\%$ in E_{max} for "high" relative to crushed oxycodone</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>IR were experienced by 79% and 71% of patients, respectively, receiving oxycodone/naltrexone ER.</p> <p>Secondary: Secondary VAS measures were lower for crushed oxycodone/naltrexone ER compared to oxycodone IR. LS mean E_{max} for “take drug again” and “overall drug liking” ($P<0.0001$), as well as for “any drug effects,” “good drug effects,” “sleepy,” and “dizzy,” ($P<0.01$) were significantly lower with oxycodone/naltrexone ER compared to oxycodone IR. LS mean E_{max} for “bad drug effects” and “nausea” were lower and for “feel sick” were higher with oxycodone/naltrexone ER compared to oxycodone IR, but these differences were not statistically significant.</p> <p>Peak reduction in pupil diameter and AUE_{0-2h} were significantly less with oxycodone/naltrexone ER compared to oxycodone IR ($P<0.0001$).</p> <p>The absorption of oxycodone was delayed with oxycodone/naltrexone ER compared to oxycodone IR (median T_{max}, 1.6 vs 0.5 hours post-dose, respectively). The AUC_{inf} was 20% lower and the mean C_{max} was approximately 30% lower for oxycodone/naltrexone ER compared to oxycodone IR. The half-life of oxycodone was similar between the two groups (~4 hours).</p> <p>The absorption of noroxycodone was more rapid with oxycodone/naltrexone ER compared to oxycodone IR (median T_{max}: 2.1 vs 4.1 hours post-dose, respectively). The mean C_{max} for noroxycodone was 52% greater and the AUC_{inf} was approximately 8% greater with oxycodone/naltrexone ER compared to oxycodone IR. The half-life of noroxycodone was similar between the two groups (~7 hours).</p> <p>The mean C_{max} for naltrexone was 4.372 ng/mL with</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>oxycodone/naltrexone ER. The median T_{max} was 18 minutes post-dose. The mean AUC_{inf} was 10.7 ng·h/mL and the half-life was 3.6 hours.</p> <p>Adverse events characteristic of opioids (i.e. euphoric mood, somnolence, nausea) were reported less frequently with oxycodone/naltrexone ER than with oxycodone IR, particularly for euphoric mood (33 vs 84%, respectively). No clinically significant abnormalities were seen in vital signs, ECG, physical examination, laboratory values, oxygen saturation, or end-tidal carbon dioxide.</p> <p>Nasal tract–related adverse events were infrequent and mild in intensity, and occurred more commonly with oxycodone IR. Nasal irritation scores were low for all treatments, but were numerically higher with oxycodone IR. Mean E_{max} and AUE_{0-2h} for burning, need to blow nose, and facial pain/pressure were slightly higher with oxycodone IR compared to oxycodone/naltrexone ER and placebo.</p>
<p>Backonja et al^{2,8*}</p> <p>Oxycodone 20 mg and naltrexone 2.4 mg IV in solution</p> <p>vs</p> <p>oxycodone 20 mg IV</p> <p>vs</p> <p>placebo (0.9% sodium chloride) IV</p> <p>This trial consisted of four</p>	<p>AC, DB, PC, RCT, XO</p> <p>Healthy non-dependent recreational opioid users aged 18 to 55 years without a history or current diagnosis of substance abuse or dependence, who are not seeking treatment for</p>	<p>N=29</p> <p>Three treatment phases</p>	<p>Primary:</p> <p>LS mean E_{max} and AUE_{0-2h} for “drug liking” and “high” via the VAS</p> <p>Secondary:</p> <p>VAS measures for “take drug again,” “overall drug liking,” “good drug effects,” “bad drug effects,” “any drug</p>	<p>Primary:</p> <p>LS mean E_{max} (95% CI) for “drug liking” via the VAS were 58.2 (54.7 to 61.7), 92.4 (88.9 to 95.9), and 52.2 (48.7 to 55.7) for oxycodone 20 mg and naltrexone 2.4 mg IV, oxycodone 20 mg IV, and placebo, respectively ($P \leq 0.001$ for oxycodone and naltrexone vs oxycodone IR; $P \leq 0.05$ for all oxycodone and naltrexone vs placebo; $P \leq 0.0001$ for oxycodone vs placebo).</p> <p>LS mean E_{max} (95% CI) for “high” via the VAS were 17.2 (11.3 to 23.1), 93.1 (87.2 to 99.1), and 3.4 (-2.5 to 9.4) for oxycodone 20 mg and naltrexone 2.4 mg IV, oxycodone 20 mg IV, and placebo, respectively ($P \leq 0.001$ for oxycodone and naltrexone vs oxycodone IR; $P \leq 0.05$ for all oxycodone and naltrexone vs placebo; $P \leq 0.0001$ for oxycodone vs placebo).</p> <p>Reductions $\geq 30\%$ and $\geq 50\%$ in E_{max} for “drug liking” relative to</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
phases: a screening phase, a naloxone challenge, a drug discrimination phase, and a treatment phase. The treatment phase consisted of three single-dose phases separated by a washout period of ≥ 5 days.	substance-related disorders, who have used opioids for non-therapeutic purposes at least 10 times in the past year and at least once in the past eight weeks, and who have used opioids either intranasally at least three times or intravenously at least once in the past year		effects, "feel sick," "nausea," "sleepy," and "dizzy," pupillometry, safety, plasma oxycodone and naltrexone C_{5min} , T_{max} , AUC_{0-2h} , AUC_{inf} , and half-life	<p>oxycodone 20 mg IV were experienced by 90% and 83% of patients, respectively, receiving oxycodone 20 mg and naltrexone 2.4 mg IV.</p> <p>Reductions $\geq 30\%$ and $\geq 50\%$ in E_{max} for "high" relative to oxycodone 20 mg IV were experienced by 93% of patients receiving oxycodone 20 mg and naltrexone 2.4 mg IV.</p> <p>Secondary: Secondary VAS measures were lower for oxycodone 20 mg and naltrexone 2.4 mg IV and placebo compared to oxycodone 20 mg IV ($P \leq 0.001$ for oxycodone and naltrexone vs oxycodone alone for all measures, except "bad drug effects").</p> <p>LS mean E_{max} for "take drug again," "overall drug liking," and "good drug effects" were significantly lower with oxycodone 20 mg and naltrexone 2.4 mg IV compared to oxycodone 20 mg IV ($P < 0.001$).</p> <p>Pupillometry results showed that oxycodone 20 mg and naltrexone 2.4 mg IV had less physiologic opioid effects than oxycodone 20 mg IV, and that both had more opioid effects than placebo; those receiving oxycodone 20 mg IV experienced more significant constriction of the pupils compared to oxycodone 20 mg and naltrexone 2.4 mg IV and placebo. Examination of pupillometry demonstrated that E_{max} for pupil constriction from baseline with oxycodone 20 mg and naltrexone 2.4 mg IV was significantly greater than with oxycodone 20 mg IV ($P < 0.001$).</p> <p>The median T_{max} for oxycodone was similar for oxycodone 20 mg and naltrexone 2.4 mg IV and oxycodone 20 mg IV (0.15 hours post-dose). The mean AUC_{inf} was comparable for oxycodone 20 mg and naltrexone 2.4 mg IV and oxycodone 20 mg IV (393.7 vs 420.3 ng·h/mL, respectively). The mean C_{5min} were 140.6 ng/mL for oxycodone 20 mg and naltrexone 2.4 mg IV and 134.6 ng/mL</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>for oxycodone 20 mg IV. The mean half-life was similar between groups (3.66 hours).</p> <p>The mean C_{5min} for naltrexone was 12.8 ng/mL with oxycodone 20 mg and naltrexone 2.4 mg IV. The median T_{max} was nine minutes post-dose. The mean AUC_{inf} was 17.2 ng·h/mL, and the half-life was 2.82 hours.</p> <p>More patients taking oxycodone IV reported TEAEs compared to patients taking oxycodone 20 mg and naltrexone 2.4 mg IV or placebo. No serious adverse events were reported, and no clinically significant abnormalities were seen in oxygen saturation or end-tidal carbon dioxide.</p>

*Trial is registered on ClinicalTrials.gov

†No comparative data provided for placebo

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, IV=intravenously

Study abbreviations: AC=active-controlled, AUC_{0-2h} =area under the curve up to 2 hours after dose, AUE_{0-2h} =area under the effect curve up to 2 hours after dose, AUC_{inf} =area under the curve extrapolated to infinity, AUC_{last} =area under the curve up to the time of the last quantifiable concentration, BMI=body mass index, BPI=Brief Pain Inventory, BPI-sf=Brief Pain Inventory-Short Form, CI=confidence interval, CLBP=chronic lower back pain, C_{5min} =plasma concentration at five minutes, C_{max} =maximum concentration, CNCP=chronic non-cancer pain, COMM[™]=Current Opioid Misuse Measure[™], COWS=Clinical Opiate Withdrawal Scale, DB=double-blind, DD=double-dummy, ECG=electrocardiogram, E_{max} =peak effect, LS=least squares, MC=multicenter, OL=open-label, PC=placebo-controlled, PGA=Patient's Global Assessment, RCT=randomized controlled trial, RMDQ=Roland Morris Disability Questionnaire, SD=standard deviation, TDA=willingness to "take drug again", TEAE=treatment-emergent adverse event, T_{max} =time to maximum concentration, VAS=visual analog scale, XO=crossover

Pharmacokinetics/Pharmacogenomics

Absorption

The oral bioavailability of oxycodone is 60 to 87%. Dose proportionality of oxycodone has been established for Troxyca[®] ER (oxycodone/naltrexone extended-release) using oxycodone IR 5 mg, 15 mg and 30 mg tablets based on extent of absorption (AUC).¹

The median time to maximum concentration (T_{max}) of oxycodone for Troxyca[®] ER (oxycodone/naltrexone extended-release) is approximately 12 hours post-dose (range, 8 to 16 hours). The AUC is equivalent to that of oxycodone IR tablets; the mean maximum concentration (C_{max}) is reduced by approximately 67% compared to oxycodone IR tablets. Steady state was reached within 48 hours with Troxyca[®] ER (oxycodone/naltrexone extended-release), whereas it is reached in 18 to 24 hours with oxycodone IR tablets. The C_{max} of oxycodone for Troxyca[®] ER (oxycodone/naltrexone extended-release) increased by 86% and the AUC over 24 hours (AUC_{0-24}) increased by 168% at steady state on day 5 compared to day 1. The half-life after a single dose is approximately 7.2 hours and does not change after multiple doses.¹

An analysis of pharmacokinetic results from phase I single-dose studies with Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules 20 mg/2.4 mg to 80 mg/9.6 mg showed that oxycodone AUC and C_{max} increased in a dose proportional manner. Following single-dose administration of intact Troxyca[®] ER (oxycodone/naltrexone extended-release), naltrexone was undetected (limit of quantitation, 4 pg/mL); however, a metabolite of naltrexone, 6- β -naltrexol, was observed in 54% of patients with a median concentration of 7.8 pg/mL and a range of 4.1 to 45.4 pg/mL (limit of quantitation, 4 pg/mL).¹

Naltrexone plasma concentrations were undetected in 78% of the samples collected from patients in phase III studies. In the samples with measurable naltrexone concentrations, the median concentration was 11.2 pg/mL and the range was 4.1 to 1090 pg/mL. At least one measureable naltrexone concentration was observed in 34% of patients.

Plasma concentrations of 6- β -naltrexol were undetected in 40% of the samples collected from patients in phase III studies. In the samples with measurable 6- β -naltrexol concentrations, the median concentration was 42.5 pg/mL and the range was 4.1 to 7320 pg/mL. At least one measureable 6- β -naltrexol level was observed in 73% of patients.

Distribution

The steady-state volume of distribution (V_{ss}) for oxycodone given intravenously is 2.6 L/kg. Plasma protein binding of oxycodone is approximately 45%. Oxycodone has been found to be excreted in breast milk.¹

The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 L. In vitro tests with human plasma show that the plasma protein binding of naltrexone is 21% over the therapeutic dose range.¹

Metabolism

Oxycodone is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The primary pathway of metabolism is CYP3A-mediated N-demethylation to an inactive metabolite from noroxycodone. A minor pathway of metabolism is CYP2D6-mediated O-demethylation to an active metabolite, oxymorphone. Oxymorphone is present in the plasma only in low concentrations.¹

The systemic clearance of naltrexone after intravenous administration is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests that naltrexone is a highly extracted drug (>98% metabolized) and that extrahepatic sites of metabolism exist. The major metabolite of naltrexone is 6- β -naltrexol, which is formed by cytosolic NADPH-requiring enzymes. Two other minor metabolites are 2-hydroxy-3-methoxy-6- β -naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to

form additional metabolites. The activity of naltrexone is believed to be due to both naltrexone and 6- β -naltrexol.¹

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%, conjugated oxycodone up to 50%, free oxymorphone 0%, conjugated oxymorphone $\leq 14\%$; both free and conjugated noroxycodone have been found in the urine but are not quantified. The total plasma clearance of oxycodone is 0.8 L/min and the apparent elimination half-life following the administration of oxycodone IR is 3.5 to 4 hours. Following oral administration of Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules, the apparent elimination half-life of oxycodone is approximately 7.2 hours and steady state is reached within 48 hours upon twice-daily dosing with Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules approximately 12 hours apart.¹

Naltrexone is excreted primarily in the urine as conjugates of naltrexone and 6- β -naltrexol. The renal clearance for naltrexone ranges from 30 to 127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6- β -naltrexol ranges from 230 to 369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for $<2\%$ of an oral dose; urinary excretion of unchanged and conjugated 6- β -naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling. The mean elimination half-life values for naltrexone and 6- β -naltrexol are four hours and 13 hours, respectively.¹

Food Effects

When a single dose of Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules are administered in fasted state or after a high-fat meal, or when the contents of Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules are sprinkled on one tablespoon of applesauce and administered in a fasted state, oxycodone pharmacokinetics are unaffected, and AUC, C_{\max} , and T_{\max} values are similar. Naltrexone plasma concentrations also remain undetectable (below the limit of quantitation, 4 pg/mL); this suggests that administration of Troxyca[®] ER (oxycodone/naltrexone extended-release) capsules with food or sprinkling of the pellets on applesauce does not affect sequestration of naltrexone. The C_{\max} of 6- β -naltrexol was 30 pg/mL, observed at 120 hours after administration of Troxyca[®] ER (oxycodone/naltrexone extended-release) after a high-fat meal.¹

Effects of Tampering

After oral administration, oxycodone plasma exposures were comparable between crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) and corresponding dosages of crushed oxycodone IR. Oxycodone C_{\max} for crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) was similar to that for equivalent doses of crushed oxycodone IR, but was approximately four times greater than that of intact Troxyca[®] ER (oxycodone/naltrexone extended-release). Intact Troxyca[®] ER (oxycodone/naltrexone extended-release) had a longer T_{\max} for oxycodone (12.1 hours) compared to crushed treatments. The majority of subjects had no observable plasma exposures to naltrexone, and most concentrations were below the limit of detection. The mean half-life for naltrexone for crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) ranged from 5.4 to 5.6 hours.⁶

After intranasal administration, the median T_{\max} for oxycodone was longer for crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) compared to corresponding doses of crushed oxycodone IR (1.6 vs 0.5 hours, respectively). The overall plasma exposure was 20% lower with crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) compared to crushed oxycodone IR. In addition, the mean C_{\max} for oxycodone was approximately 30% lower for crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) compared to crushed oxycodone IR. Both treatments had comparable mean half-life values of approximately 7 hours. After intranasal administration of crushed Troxyca[®] ER (oxycodone/naltrexone extended-release) 30 mg/3.6 mg, the mean C_{\max} for naltrexone was 4.372 ng/mL, with a median T_{\max} of 18 minutes.⁷

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 (ultrarapid 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.¹⁵

Table 3. Pharmacokinetics^{1,16}

Generic Name	T _{max} (hours)	Duration (hours)	Renal Clearance (L/h)	Active Metabolites	Serum Half-Life (hours)
Oxycodone/ naltrexone	12	12	48 (oxycodone) 1.8 to 7.6 (naltrexone)	Noroxycodone, oxymorphone, noroxymorphone (oxycodone) 6-β-naltrexol (naltrexone)	7.2 (oxycodone) 4.0 (naltrexone)

Special Populations**Table 4. Special Populations¹**

Population	Precaution
Elderly	No evidence of overall differences in safety or efficacy have been observed between elderly and younger adult patients.
Renal Dysfunction	Dose initiation of Troxyca [®] ER (oxycodone/naltrexone extended-release) should follow a conservative approach in patients with renal impairment, as there is a potential for differential increase in naltrexone exposure compared to oxycodone exposure. When administering Troxyca [®] ER (oxycodone/naltrexone extended-release) to patients with renal impairment, monitor patients closely for signs of central nervous system (CNS) or respiratory depression due to elevated levels of oxycodone and for signs of withdrawal due to elevated levels of naltrexone and adjust the dose based on the clinical response. Since naltrexone and its primary metabolite are primarily excreted in the urine, plasma concentrations may be increased in patients with renal impairment.
Hepatic Dysfunction	Dose initiation of Troxyca [®] ER (oxycodone/naltrexone extended-release) should follow a conservative approach in patients with hepatic impairment, as there is a potential for differential increase in naltrexone exposure compared to oxycodone exposure. When administering Troxyca [®] ER (oxycodone/naltrexone extended-release) to patients with hepatic impairment, monitor patients closely for signs of

Population	Precaution
	CNS or respiratory depression due to elevated levels of oxycodone and for signs of withdrawal due to elevated levels of naltrexone and adjust the dose based on the clinical response. Oxycodone is extensively metabolized by the liver, and its clearance may decrease in patients with hepatic impairment. An increase in naltrexone AUC has been reported in patients with compensated and decompensated cirrhosis compared to those with normal liver function.
Pregnancy/Lactation	<p>The prolonged use of opioids during pregnancy may result in physical dependence in the neonate and neonatal opioid withdrawal syndrome after birth. Opioids cross the placenta and may result in respiratory depression and psycho-physiologic effects in neonates. There are no data available for Troxyca[®] ER (oxycodone/naltrexone extended-release) in pregnant women regarding potential for birth defects or miscarriage. The use of Troxyca[®] ER (oxycodone/naltrexone extended-release) is not recommended during and immediately prior to labor, when the use of shorter acting analgesics or other analgesic agents is more appropriate.</p> <p>Oxycodone is present in breast milk; lactation studies have not been conducted with extended-release formulations of oxycodone, including Troxyca[®] ER (oxycodone/naltrexone extended-release).</p>
Children	Safety and efficacy of Troxyca [®] ER (oxycodone/naltrexone extended-release) have not been established in patients below the age of 18 years.
Gender/Race	There are no clinically significant differences in oxycodone pharmacokinetics following oral administration of Troxyca [®] ER (oxycodone/naltrexone extended-release) to males or females. No specific dosage adjustment is recommended for the initiation or maintenance of Troxyca [®] ER (oxycodone/naltrexone extended-release) doses based on the sex of the patient.

Dosage Forms

Table 5. Availability, Storage and Handling¹

Dosage Form	Strength	Special Handling or Storage
Extended-release capsule	10 mg/1.2 mg 20 mg/2.4 mg 30 mg/3.6 mg 40 mg/4.8 mg 60 mg/7.2 mg 80 mg/9.6 mg	<p>Store at 25°C (77°F); excursions between 15° and 30°C (59° and 86°F) are permitted.</p> <p>Dispense and store in tight, light-resistant container with child-resistant closure.</p>

Dosage Range**Table 6. Dosing and Administration¹**

Adult Dose	Pediatric Dose	Renal Dose	Hepatic Dose
<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 not opioid-tolerant: 10 mg/1.2 mg by mouth every 12 hours. Maintenance: Titrate to a dose that provides adequate analgesia and minimizes adverse reactions; the total daily dose may be adjusted by 20 mg/2.4 mg every two to three days as needed based on efficacy, safety, and tolerability.	Safety and efficacy in pediatric patients have not been established.	No specific recommendations.	No specific recommendations.

For patients converting from a different opioid to Troxyca[®] ER (oxycodone/naltrexone extended-release), the manufacturer provides a table to estimate a total oxycodone daily dose.

Table 7. Opioid Conversion Factors¹

Opioid	Approximate Oral Conversion Factor*
Codeine	0.1
Hydrocodone	0.67
Hydromorphone	2.67
Methadone	See dosing considerations
Morphine	0.67
Oxycodone	1
Tramadol	See dosing considerations
Transdermal fentanyl	See dosing considerations

*These conversion factors may be used to convert from other opioids to Troxyca[®] ER (oxycodone/naltrexone extended-release), but cannot be used to convert from Troxyca[®] ER (oxycodone/naltrexone extended-release) to other opioids.

Dosing Considerations:**Conversion from other oral oxycodone formulations to Troxyca[®] ER (oxycodone/naltrexone extended-release)**

Patients receiving other oral oxycodone formulations may be converted to Troxyca[®] ER (oxycodone/naltrexone extended-release) by administering one half of the patient's total daily oral oxycodone dose as Troxyca[®] ER (oxycodone/naltrexone extended-release) every 12 hours.¹

Conversion from other opioids to Troxyca[®] ER (oxycodone/naltrexone extended-release)

Discontinue all other around-the-clock opioid drugs when Troxyca[®] ER (oxycodone/naltrexone extended-release) therapy is initiated.¹

There is inter-patient variability in the relative potency of opioid drugs and formulations. Therefore, a conservative approach is advised when determining the total daily dosage of Troxyca[®] ER (oxycodone/naltrexone extended-release). It is safer to underestimate a patient's total daily dose of

Troxyca® ER (oxycodone/naltrexone extended-release) and provide rescue medication than to overestimate the total daily dose of oxycodone and manage an adverse reaction due to overdose.¹

In a clinical trial of Troxyca® ER (oxycodone/naltrexone extended-release) with an open-label titration period, patients were converted from their prior opioid to Troxyca® ER (oxycodone/naltrexone extended-release) using the conversion factors in Table 7.¹

Conversion from methadone to Troxyca® ER (oxycodone/naltrexone extended-release)

Close monitoring 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.¹

Conversion from tramadol to Troxyca® ER (oxycodone/naltrexone extended-release)

Tramadol has both serotonergic and opioid activity, and there has been no systematic assessment of this conversion. The recommended starting dose of Troxyca® ER (oxycodone/naltrexone extended-release) in patients receiving tramadol is 10 mg/1.2 mg every 12 hours.¹

Conversion from transdermal fentanyl to Troxyca® ER (oxycodone/naltrexone extended-release)

Treatment with Troxyca® ER (oxycodone/naltrexone extended-release) can be initiated after the transdermal fentanyl patch has been removed for at least 18 hours. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg/1.2 mg of Troxyca® ER (oxycodone/naltrexone extended-release) every 12 hours for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to Troxyca® ER (oxycodone/naltrexone extended-release), as there is limited documented experience with this conversion.¹

Conversion from transdermal buprenorphine to Troxyca® ER (oxycodone/naltrexone extended-release)

There has been no systematic assessment of this conversion. The recommended starting dose of Troxyca® ER (oxycodone/naltrexone extended-release) in patients receiving transdermal buprenorphine is 10 mg/1.2 mg every 12 hours.¹

Discontinuation of Troxyca® ER (oxycodone/naltrexone extended-release)

When a patient no longer requires therapy with Troxyca® ER (oxycodone/naltrexone extended-release), taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Troxyca® ER (oxycodone/naltrexone extended-release).¹

Precautions

Boxed Warning for Troxyca® ER (oxycodone/naltrexone extended-release)¹

WARNING

Addiction, Abuse and Misuse

Troxyca® ER (oxycodone/naltrexone 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.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow Troxyca® ER (oxycodone/naltrexone extended-release) capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving Troxyca® ER (oxycodone/naltrexone extended-release) can cause rapid release and absorption of a potentially fatal dose of oxycodone.

WARNING

Accidental Ingestion

Accidental ingestion of Troxyca[®] ER (oxycodone/naltrexone extended-release), especially by children, can result in fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Troxyca[®] ER (oxycodone/naltrexone 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.

CYP3A4 Inhibitors or Inducers

The concomitant use of Troxyca[®] ER (oxycodone/naltrexone extended-release) with all CYP3A4 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 CYP3A4 inducer may result in an increase in oxycodone plasma concentrations. Monitor patients receiving Troxyca[®] ER (oxycodone/naltrexone extended-release) and any CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of Troxyca[®] ER (oxycodone/naltrexone extended-release) and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Table 8. Warnings/Precautions¹

Warning/ Precaution	<p>Addiction, abuse and misuse; as an opioid, Troxyca[®] ER (oxycodone/naltrexone extended-release) exposes users to the risks of addiction, abuse and misuse. As extended-release products such as Troxyca[®] ER (oxycodone/naltrexone extended-release) deliver the opioid over an extended period of time, there is a greater risk of overdose and death due to the larger quantity of oxycodone present. Although the risk of addiction in any individual is not known, it can occur in patients appropriately prescribed Troxyca[®] ER (oxycodone/naltrexone extended-release) at the recommended dosages. Patients at increased risk may be prescribed opioids, but use in such patients necessitates intensive counseling regarding the risks and appropriate use of Troxyca[®] ER (oxycodone/naltrexone extended-release), along with intensive monitoring for signs of addiction, abuse, and misuse.</p> <p>Abuse or misuse of Troxyca[®] ER (oxycodone/naltrexone extended-release) by cutting, breaking, chewing, crushing, or dissolving the pellets in Troxyca[®] ER (oxycodone/naltrexone extended-release) and then swallowing, snorting or injecting will result in the uncontrolled delivery of oxycodone and may result in overdose and death. Misuse or abuse of Troxyca[®] ER (oxycodone/naltrexone extended-release) by these methods may also release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals.</p> <p>Neonatal opioid withdrawal syndrome; prolonged use of oxycodone during pregnancy can result in withdrawal signs in the neonate. 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 appropriate treatment will be available.</p>
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	<p>Risks due to interactions with CNS depressants; hypotension, profound sedation, coma or respiratory depression may result if oxycodone is used concomitantly with alcohol or other CNS depressants (e.g., benzodiazepines, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids). When considering use in patients taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance developed to the CNS depression. Use of alcohol or illicit drugs that cause CNS depression should also be evaluated. This agent should be started at a lower dosage and patients should be monitored for sedation, respiratory depression and hypotension.</p> <p>Risk of life-threatening respiratory depression in the elderly, cachectic and debilitated patients; life-threatening respiratory depression is more likely to occur in elderly, cachectic or debilitated patients as they have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor these patients closely when initiating and titrating Troxyca[®] ER (oxycodone/naltrexone extended-release) and when this agent is given concomitantly with other drugs that depress respiration.</p> <p>Adrenal insufficiency; cases of adrenal insufficiency have been reported with opioid use, often after at least one month of use. Presentation of adrenal insufficiency may include nonspecific symptoms, such as 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 and treat with physiologic replacement of corticosteroids. The patient should be weaned off of the opioid and corticosteroid treatment should be continued until adrenal function recovers.</p> <p>Severe hypotension; Troxyca[®] ER (oxycodone/naltrexone extended-release) 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 is already compromised by a reduced blood volume or concomitant CNS depressant drugs. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Troxyca[®] ER (oxycodone/naltrexone extended-release). Avoid use in patients with circulatory shock, as Troxyca[®] ER (oxycodone/naltrexone extended-release) may cause vasodilation that further reduces cardiac output and blood pressure in these patients.</p> <p>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), Troxyca[®] ER (oxycodone/naltrexone extended-release) may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor these patients for signs of sedation and respiratory depression, particularly when initiating therapy with Troxyca[®] ER (oxycodone/naltrexone extended-release).</p> <p>Increased risk of seizures in patients with seizure disorders; Troxyca[®] ER (oxycodone/naltrexone extended-release) may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during treatment.</p> <p>Withdrawal; 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. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.</p>
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	Consuming Troxyca® ER (oxycodone/naltrexone extended-release) that has been altered by crushing, chewing, or dissolving the pellets can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals. Symptoms of withdrawal usually appear within five minutes of ingestion of naltrexone, may last for up to 48 hours, and may include mental status changes, restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis.
	When discontinuing Troxyca® ER (oxycodone/naltrexone extended-release), gradually taper the dosage; do not abruptly discontinue this agent.
	Risks of driving and operating machinery; Troxyca® ER (oxycodone/naltrexone extended-release) may impair the mental or physical abilities necessary to perform potentially hazardous activities, such as driving a car or operating machinery. Patients should be warned not to drive or operate dangerous machinery unless they are tolerant to the effects of this agent and know how they will be affected by it.
	Risks of concomitant use or discontinuation of CYP3A4 inhibitors and inducers; concomitant use of Troxyca® ER (oxycodone/naltrexone extended-release) with a CYP3A4 inhibitor may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, particularly when an inhibitor is added after a stable dose of Troxyca® ER (oxycodone/naltrexone extended-release) is achieved. Similarly, discontinuation of a CYP3A4 inducer in patients treated with Troxyca® ER (oxycodone/naltrexone extended-release) may increase oxycodone concentrations and prolong opioid adverse reactions. Concomitant use of Troxyca® ER (oxycodone/naltrexone extended-release) with a CYP3A4 inducer or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or lead to withdrawal in a patient who had developed physical dependence to oxycodone.

Contraindications

Table 9. Contraindications¹

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

Adverse Effects

Table 10 represents adverse reactions reported in ≥2% of subjects from both the open-label and double-blind treatment periods of a phase III clinical trial for Troxyca® ER (oxycodone/naltrexone extended-release). Figures reported during the open-label titration phase are reported in the active drug column.¹

Table 10. Adverse Events¹

Adverse Event (%)	Reported Frequency	
	Active Drug, Dosing Regimen N=410 (open-label titration phase), 146 (double-blind treatment phase)	Placebo N=134
Nausea	20.5, 14.4	3.7
Constipation	14.9, 3.4	2.2

Adverse Event (%)	Reported Frequency	
	Active Drug, Dosing Regimen N=410 (open-label titration phase), 146 (double-blind treatment phase)	Placebo N=134
Vomiting	9.0, 6.2	3.0
Somnolence	9.0, 0.7	0.7
Headache	7.3, 1.4	5.2
Pruritus	6.6, 2.1	0.0
Dizziness	5.9, 4.1	0.7
Diarrhea	2.2, 5.5	4.5
Fatigue	3.2, 3.4	0.7
Dry mouth	3.2, 0.0	0.0
Abdominal pain	2.9, 1.4	6.0
Hyperhidrosis	2.4, 2.7	0.7
Hot flush	2.4, 1.4	2.2
Insomnia	2.0, 0.7	0.7
Back pain	1.2, 2.1	6.0
Drug withdrawal syndrome	1.0, 2.7	1.5
Arthralgia	0.7, 2.1	0.7
Edema, peripheral	0.7, 2.1	0.7
Muscle spasms	0.2, 2.7	0.7
Oropharyngeal pain	0.2, 2.7	0.7
Hypoesthesia	0.0, 2.1	0.0

Drug Interactions

Table 11. Drug Interactions^{1,16}

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
CNS Depressants	Major	Due to their additive pharmacologic effect, the concomitant use of opioids and other CNS depressants may 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.
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.
CYP3A4 Inducers	Major	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.
Mixed Agonist/Antagonist and Partial Agonist	Major	The use of these agents may reduce the analgesic effect of oxycodone or precipitate withdrawal symptoms. Avoid concomitant use of oxycodone with these agents.

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
Opioids		
Muscle Relaxants	Major	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and result in an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected. Decrease the dose of oxycodone and/or the muscle relaxant as necessary.
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.
Diuretics	Moderate	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure. Increase the dose of the diuretic as necessary.
Ginseng	Moderate	Concomitant use of opioids with ginseng may result in decreased efficacy of analgesia of opioids.
Kava	Moderate	Concomitant use of opioids with kava may result in increased CNS depression.
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.
Anticholinergic Drugs	Unknown	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when using opioids concomitantly with anticholinergic agents.

*Severity rating per Micromedex

Patient Monitoring Guidelines

Before starting therapy with an opioid, individuals should be evaluated for potential signs of addiction, abuse or misuse of medications; risks are increased in patients with a personal or family history of substance abuse or mental illness, but the potential for these risks should not prevent the proper management of pain. If therapy with an opioid is 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.¹

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

- respiratory depression and sedation; especially within the first 24 to 72 hours after initiating therapy and following dose increases; and particularly in high risk patients (elderly, cachectic, or debilitated patients, those with preexisting respiratory depression or otherwise significantly reduced respiratory reserve, and those who may be susceptible to the intracranial effects of CO₂ retention)

- exacerbation of biliary tract disease
- hypotension; in ambulatory patients and in those whose ability to maintain blood pressure has been compromised; especially after initiating therapy or titrating the dose
- worsened seizure control; in patients with a history of seizure disorders

References

1. TROXYCA® ER [package insert]. New York (NY): Pfizer Inc; 2016 Aug.
2. TROXYCA® ER (oxycodone-naltrexone) product eDossier. Sep 2016. Pfizer Inc. Data on file.
3. Rauck RL, Hale ME, Bass A, et al. A randomized double-blind, placebo-controlled efficacy and safety study of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) for moderate-to-severe chronic low back pain treatment. *Pain*. 2015;156:1660-1669.
4. Arora S, Setnik B, Michael D, et al. A multicenter, 12-month, open-label, single-arm safety study of oxycodone-hydrochloride/naltrexone-hydrochloride extended-release capsules (ALO-02) in patients with moderate-to-severe chronic noncancer pain. *J Opioid Manag*. 2014;10(6):423-436.
5. Embeda® [package insert]. New York (NY): Pfizer Inc; 2014 Apr.
6. Setnik B, Bass A, Bramson C, et al. Abuse Potential Study of ALO-02 (Extended-Release Oxycodone Surrounding Sequestered Naltrexone) Compared with Immediate-Release Oxycodone Administered Orally to Nondependent Recreational Opioid Users. *Pain Med*. 2016 Aug 22 [Epub ahead of print].
7. Setnik B, Bramson C, Bass A, et al. Intranasal administration of crushed ALO-02 (extended-release oxycodone with sequestered naltrexone): a randomized, controlled abuse-potential study in nondependent recreational opioid users. *J Clin Pharmacol*. 2015;55(12):1351-1361.
8. Backonja M, Webster LR, Setnik B, et al. Intravenous abuse potential study of oxycodone alone or in combination with naltrexone in nondependent recreational opioid users. *Am J Drug Alcohol Abuse*. 2016 May 21:1-11 [Epub ahead of print].
9. OxyContin® [package insert]. Stamford (CT): Purdue Pharma, LP; 2016 Dec.
10. Targiniq® ER [package insert]. Stamford (CT): Purdue Pharma, LP; 2016 Dec.
11. Xtampza® ER [package insert]. Cincinnati (OH): Patheon Pharmaceuticals; 2016 Nov.
12. U.S. Food and Drug Administration. Opioid Medications; Information on Opioid Medications [webpage on the internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2017 Jan 23 [cited 2017 Feb 1]. Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm>.
13. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017 [cited 2017 Feb 1]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
14. Brief-Egalet receives FDA approval for Arymo ER [press release on the internet]. Reuters; 2017 Jan 10 [cited 2017 Feb 1]. Available from: <http://in.reuters.com/article/idINASC09Q4B>
15. Vuilleumier PH, Stamer UM and Landau R. Pharmacogenomic considerations in opioid analgesia. *Pharmacogenomics and Personalized Medicine*. 2012;5:73-87.
16. Micromedex® Healthcare Series [database on the internet]. Cambridge (MA): Truven Health Analytics; Updated periodically [cited 2017 Feb 1]. Available from: <http://www.thomsonhc.com/>.