HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TROXYCA ER safely and effectively. See full prescribing information for TROXYCA ER.

TROXYCA® ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules, for oral use, CII
Initial U.S. Approval: 2016

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION
See full prescribing information for complete boxed warning.

- **TROXYCA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1)**
- **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 capsules whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2)**
- **Accidental ingestion of TROXYCA ER, especially by children, can result in fatal overdose of oxycodone. (5.2)**
- **Prolonged use of TROXYCA ER 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. (5.3)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in fatal overdose of oxycodone from TROXYCA ER. (5.4)**

----------INDICATIONS AND USAGE----------
TROXYCA ER is a combination opioid agonist/opioid antagonist product indicated 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. (1)

Limitations of Use
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve TROXYCA ER 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. (1)
- TROXYCA ER is not indicated as an as-needed (prn) analgesic. (1)

----------DOSAGE AND ADMINISTRATION----------
- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- TROXYCA ER 60 mg/7.2 mg and 80 mg/9.6 mg capsules, single doses of TROXYCA ER greater than 40 mg/4.8 mg, or a total daily dose greater than 80 mg/9.6 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow TROXYCA ER capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. (2.1, 2.5)
- Instruct patients not to crush, chew, or dissolve the pellets in the capsule to avoid the risk of release and absorption of a potentially fatal dose of oxycodone and to avoid release of sequestered naltrexone that could precipitate opioid withdrawal. (2.1, 2.5, 5.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with the 10 mg/1.2 mg capsule every 12 hours. (2.1, 2.2)
- Do not abruptly discontinue TROXYCA ER. (2.4, 5.12)

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release capsules (oxycodone hydrochloride/naltrexone hydrochloride): 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 and 80 mg/9.6 mg. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of TROXYCA ER in patients with circulatory shock. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of TROXYCA ER in patients with impaired consciousness or coma. (5.9)

----------ADVERSE REACTIONS----------
Most common adverse reactions: nausea, constipation, vomiting, headache, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CNS Depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects and monitor closely. (5.5, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue TROXYCA ER if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with TROXYCA ER because they may reduce analgesic effect of TROXYCA ER or precipitate withdrawal symptoms. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Avoid TROXYCA ER in patients taking MAOIs or within 14 days of stopping such treatment. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (5.3, 8.1)
- Lactation: Not recommended. (8.2)
- Geriatric patients: Start at the low end of the dosing range and monitor closely for respiratory depression. (5.6, 8.5)
- Hepatic Impairment: Monitor patients closely for CNS or respiratory depression and for signs of withdrawal. (8.6, 12.3)
- Renal Impairment: Monitor patients closely for CNS or respiratory depression and for signs of withdrawal. (8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION.

Addiction, Abuse, and Misuse

TROXYCA ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing TROXYCA ER, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of TROXYCA ER. Monitor for respiratory depression, especially during initiation of TROXYCA ER or following a dose increase. Instruct patients to swallow TROXYCA ER capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving TROXYCA ER can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of TROXYCA ER 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 *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of TROXYCA ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentrations. Monitor patients receiving TROXYCA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.4), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

1 INDICATIONS AND USAGE

TROXYCA ER is indicated 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.

Limitations of Use:

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve TROXYCA ER 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.
- TROXYCA ER is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

TROXYCA ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

TROXYCA ER 60 mg/7.2 mg and 80 mg/9.6 mg capsules, single doses of TROXYCA ER greater than 40 mg/4.8 mg, or a total daily dose greater than 80 mg/9.6 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid-tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with TROXYCA ER and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

Instruct patients to swallow TROXYCA ER capsules whole *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving the pellets in TROXYCA ER capsules will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

Instruct patients who are unable to swallow TROXYCA ER capsules to sprinkle the capsule contents on applesauce and immediately swallow without chewing *[see Dosage and Administration (2.5)]*.

Administer TROXYCA ER orally every 12 hours.

2.2 Initial Dosing

Use of TROXYCA ER as the First Opioid Analgesic (opioid-naïve patients)
Initiate treatment with TROXYCA ER with 10 mg/1.2 mg capsule orally every 12 hours.

Use of TROXYCA ER in Patients who are not Opioid-Tolerant (opioid-non-tolerant patients)
The starting dose for patients who are not opioid-tolerant is TROXYCA ER 10 mg/1.2 mg capsule orally, every 12 hours.

Use of higher starting doses in patients who are not opioid-tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.2)]*.

Conversion from Other Oral Oxycodone HCl Formulations to TROXYCA ER
Patients receiving other oral oxycodone HCl formulations may be converted to TROXYCA ER by administering one half of the patient's total daily oral oxycodone HCl dose as TROXYCA ER every 12 hours.

Conversion from Other Opioids to TROXYCA ER
Discontinue all other around-the-clock opioid drugs when TROXYCA ER therapy is initiated.

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. It is safer to underestimate a patient's 24-hour TROXYCA ER dosage and provide rescue medication (e.g., immediate-release oxycodone) than to overestimate the 24-hour oxycodone dosage and manage an adverse reaction due to overdose.

In a TROXYCA ER clinical trial with an open-label titration period, patients were converted from their prior opioid to TROXYCA ER using Table 1.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** TROXYCA ER.
- The table **cannot** be used to convert **from** TROXYCA ER **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

To calculate the estimated TROXYCA ER dose using Table 1:

- Calculate the approximate total daily oral oxycodone dose
    - For patients on a single opioid, multiply the current total daily dose of the opioid by the appropriate conversion factor listed in Table 1.
    - For patients on a regimen of more than one opioid, use Table 1 to calculate the total daily oral oxycodone dose for each opioid and sum the totals.

- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products for calculating the approximate total daily oral oxycodone dose.
- Reduce the estimated total daily oxycodone dose by 50% to obtain the daily dose of TROXYCA ER.
- Divide the daily dose in half to obtain the every 12-hour dose of TROXYCA ER.
- After conversion, if the total daily opioid requirement is ≤20 mg per day of oral oxycodone, initiate therapy with TROXYCA ER 10 mg/1.2 mg every 12 hours (i.e., TROXYCA ER 20 mg per day).
- Always round the dose down, if necessary, to the appropriate TROXYCA ER strength(s) available.
- Provide rescue medication as needed (e.g., immediate-release oxycodone).

Table 1. Conversion Factors to TROXYCA ER[1]

Prior Oral Opioid	Approximate Oral Conversion Factor
Codeine (including combination drugs)	0.1
Hydrocodone (including combination drugs)	0.67
Hydromorphone	2.67
Methadone	See note on conversion below
Morphine	0.67
Oxycodone (including combination drugs)	1
Tramadol	See note on conversion below
Transdermal fentanyl	See note on conversion below

[1] Use this formula to calculate total daily dose of TROXYCA ER: mg/day prior opioid × conversion factor = mg/day TROXYCA ER

Example conversion from a single opioid to TROXYCA ER:

- **Step 1:** Sum the total daily dose of the prior opioid. For example, extended-release hydrocodone 30 mg twice daily = 60 mg total daily dose of hydrocodone.
- **Step 2:** Calculate the equivalent dose of oral oxycodone based on the total daily dose of the current opioid using Table 1. In this example, 60 mg total daily dose of hydrocodone × 0.67 (conversion factor) = 40.2 mg of oral oxycodone daily.
- **Step 3:** Reduce the dose by 50% and divide in half to obtain the every 12-hour dose of TROXYCA ER. In this example, the total daily dose would be 20 mg, and the final dosing regimen would be TROXYCA ER 10 mg/1.2 mg every 12 hours.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to TROXYCA ER.

Conversion from Transdermal Fentanyl to TROXYCA ER
Treatment with TROXYCA ER 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 every 12 hours for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to TROXYCA ER, as there is limited documented experience with this conversion.

Conversion from Transdermal Buprenorphine to TROXYCA ER
There has been no systematic assessment of this conversion. The recommended starting dose of TROXYCA ER in patients receiving transdermal buprenorphine is 10 mg/1.2 mg every 12 hours.

Conversion from Tramadol to TROXYCA ER
Tramadol has both serotonergic and opioid activity, and there has been no systematic assessment of this conversion. The recommended starting dose of TROXYCA ER in patients receiving tramadol is 10 mg/1.2 mg every 12 hours.

Conversion from Methadone to TROXYCA ER
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.

2.3 Titration and Maintenance of Therapy

Individually titrate TROXYCA ER to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving TROXYCA ER to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

Patients who experience breakthrough pain may require a dosage increase of TROXYCA ER, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the TROXYCA ER dosage. Because steady-state plasma concentrations are achieved within 48 hours, the total daily dose of TROXYCA ER may be adjusted by 20 mg/2.4 mg every 2 to 3 days as needed based on efficacy, safety, and tolerability.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours.

2.4 Discontinuation of TROXYCA ER

When a patient no longer requires therapy with TROXYCA ER, 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 *[see Warnings and Precautions (5.12), Drug Abuse and Dependence (9.3)]*.

2.5 Administration of TROXYCA ER

Instruct patients to swallow TROXYCA ER capsules intact. The capsules contain pellets that consist of oxycodone HCl and sequestered naltrexone HCl. The pellets in the capsules are not to be manipulated, i.e., crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.1)]*. Consuming TROXYCA ER capsules that have been altered by crushing, dissolving, or chewing the pellets can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals *[see Warnings and Precautions (5.12)]*.

Alternatively, the contents of the TROXYCA ER capsules (pellets) may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce. Instruct the patient to:

- Open the capsule.
- Sprinkle the pellets onto a small amount of applesauce and swallow immediately without chewing.
- Rinse the mouth to ensure all pellets have been swallowed.
- Discard the empty capsule shell after the contents have been sprinkled on applesauce.

Do not administer TROXYCA ER pellets through a nasogastric or gastric tube.

3 DOSAGE FORMS AND STRENGTHS

TROXYCA ER is available in 6 strengths as an extended-release hard gelatin capsule filled with common pellets as noted below:

Strength (oxycodone hydrochloride/ naltrexone hydrochloride)	**Description**
10 mg/1.2 mg	Hard gelatin capsule, silver opaque body with “NTO 10” printed in black ink, yellow opaque cap with “Pfizer” printed in black ink
20 mg/2.4 mg	Hard gelatin capsule, silver opaque body with “NTO 20” printed in black ink, violet opaque cap with “Pfizer” printed in white ink
30 mg/3.6 mg	Hard gelatin capsule, silver opaque body with “NTO 30” printed in black ink, fuchsia opaque cap with “Pfizer” printed in black ink
40 mg/4.8 mg	Hard gelatin capsule, silver opaque body with “NTO 40” printed in black ink, olive green opaque cap with “Pfizer” printed in black ink
60 mg/7.2 mg	Hard gelatin capsule, silver opaque body with “NTO 60” printed in black ink, green opaque cap with “Pfizer” printed in black ink
80 mg/9.6 mg	Hard gelatin capsule, silver opaque body with “NTO 80” printed in black ink, brick red opaque cap with “Pfizer” printed in black ink

4 CONTRAINDICATIONS

TROXYCA ER is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.6)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*
- Hypersensitivity (e.g., anaphylaxis) to oxycodone or naltrexone or any other components of the TROXYCA ER formulation *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

TROXYCA ER contains oxycodone, a Schedule II controlled substance. As an opioid, TROXYCA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As extended-release products such as TROXYCA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TROXYCA ER and in those who obtain the drug illicitly. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing TROXYCA ER, and monitor all patients receiving TROXYCA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as TROXYCA ER, but use in such patients necessitates intensive counseling about the risks and proper use of TROXYCA ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of TROXYCA ER by cutting, breaking, chewing, crushing, or dissolving the pellets in TROXYCA ER and then swallowing, snorting or injecting will result in the uncontrolled delivery of the oxycodone and can result in overdose and death *[see Overdosage (10)]*. Misuse or abuse of TROXYCA ER by these methods may also release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals *[see Warnings and Precautions (5.12)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing TROXYCA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact the local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TROXYCA ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of TROXYCA ER.

To reduce the risk of respiratory depression, proper dosing and titration of TROXYCA ER are essential *[see Dosage and Administration (2)]*. Overestimating the TROXYCA ER dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TROXYCA ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.4 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of TROXYCA ER with a CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.2)]*, particularly when an inhibitor is added after a stable dose of TROXYCA ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in TROXYCA ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using TROXYCA ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in TROXYCA ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of TROXYCA ER until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of TROXYCA ER with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using TROXYCA ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.5 Risks Due to Interactions with Central Nervous System Depressants

Hypotension, profound sedation, respiratory depression, coma, and death may result if TROXYCA ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids).

When considering the use of TROXYCA ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin TROXYCA ER is made, start with a lower dosage of TROXYCA ER, monitor patients for signs of respiratory depression, sedation, and hypotension, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7)]*.

5.6 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of TROXYCA ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: TROXYCA ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of TROXYCA ER *[see Warnings and Precautions (5.2)]*.

Elderly, Cachetic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating TROXYCA ER and when TROXYCA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.5)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the

opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.8 Severe Hypotension

TROXYCA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of TROXYCA ER. In patients with circulatory shock, TROXYCA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TROXYCA ER in patients with circulatory shock.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), TROXYCA ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with TROXYCA ER.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of TROXYCA ER in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

TROXYCA ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The oxycodone in TROXYCA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in TROXYCA ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during TROXYCA ER therapy.

5.12 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, including TROXYCA ER. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Consuming TROXYCA ER 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, can last for up to 48 hours, and can include mental status changes, restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration.

When discontinuing TROXYCA ER, gradually taper the dosage *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue TROXYCA ER *[see Drug Abuse and Dependence (9.3)]*.

5.13 Risks of Driving and Operating Machinery

TROXYCA ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of TROXYCA ER and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.14 Laboratory Tests and Monitoring

Naltrexone does not interfere with thin-layer, gas-liquid, or high pressure liquid chromatographic methods which may be used for the separation and detection of morphine, methadone, oxycodone, or quinine in the urine. Naltrexone may or may not interfere with enzymatic methods for the detection of opioids depending on the sensitivity and specificity of the test. Consult the test manufacturer for details.

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Withdrawal *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

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

In controlled and uncontrolled studies, the most common adverse reactions were nausea, constipation, vomiting, headache, and somnolence. The most common adverse reactions leading to discontinuation (≥1% in any of the treatment phases) were nausea, constipation, vomiting, somnolence, headache, fatigue, and dizziness.

In a randomized, placebo-controlled, double-blind study in subjects with moderate-to-severe chronic low back pain, 410 subjects received TROXYCA ER. This study utilized an enriched enrollment with a randomized withdrawal design in which subjects were titrated to effect on open-label TROXYCA ER for up to 42 days. Once their pain was controlled, 280 subjects were randomized to and received active treatment with TROXYCA ER (146 subjects) or were tapered off TROXYCA ER using a double-dummy design and treated with placebo (134 subjects) for 12 weeks.

Adverse reactions reported in ≥2% of subjects receiving TROXYCA ER in either the titration phase or maintenance phase of the placebo-controlled study are presented in Table 2.

Table 2. Adverse Drug Reactions Reported in ≥2% of Subjects Receiving TROXYCA ER in the Placebo-Controlled Study

System Organ Class	Open-Label Titration Phase TROXYCA ER (N=410)	Double-Blind Maintenance Phase TROXYCA ER (N=146)	Double-Blind Maintenance Phase Placebo (N=134)
Adverse Drug Reaction (ADR)	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders			
Abdominal pain[a]	12 (2.9)	2 (1.4)	8 (6.0)
Constipation	61 (14.9)	5 (3.4)	3 (2.2)
Diarrhea	9 (2.2)	8 (5.5)	6 (4.5)
Dry mouth	13 (3.2)	0	0
Nausea	84 (20.5)	21 (14.4)	5 (3.7)
Vomiting	37 (9.0)	9 (6.2)	4 (3.0)
General disorders and administration site conditions			
Drug withdrawal syndrome[b]	4 (1.0)	4 (2.7)	2 (1.5)
Fatigue	13 (3.2)	5 (3.4)	1 (0.7)
Edema peripheral	3 (0.7)	3 (2.1)	1 (0.7)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (0.7)	3 (2.1)	1 (0.7)
Back pain	5 (1.2)	3 (2.1)	8 (6.0)
Muscle spasms	1 (0.2)	4 (2.7)	1 (0.7)
Nervous system disorders			
Dizziness	24 (5.9)	6 (4.1)	1 (0.7)
Headache	30 (7.3)	2 (1.4)	7 (5.2)
Hypoesthesia	0	3 (2.1)	0
Somnolence[c]	37 (9.0)	1 (0.7)	1 (0.7)
Psychiatric disorders			
Insomnia	8 (2.0)	1 (0.7)	1 (0.7)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1 (0.2)	4 (2.7)	1 (0.7)
Skin and subcutaneous tissue disorders			
Hyperhidrosis[d]	10 (2.4)	4 (2.7)	1 (0.7)
Pruritus[e]	27 (6.6)	3 (2.1)	0
Vascular disorders			
Hot flush[f]	10 (2.4)	2 (1.4)	3 (2.2)

a. Abdominal pain also includes Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, and Gastrointestinal pain.
b. Drug withdrawal syndrome ADR includes Drug withdrawal syndrome and Withdrawal syndrome MedDRA Preferred Terms or a score of greater than or equal to 13 on the Clinical Opiate Withdrawal Scale.
c. Somnolence also includes Sedation.
d. Hyperhidrosis also includes Cold sweat.
e. Pruritus also includes Pruritus generalized.
f. Hot flush also includes Flushing.

An additional 395 subjects received at least one dose of TROXYCA ER in an open-label, 12-month safety study of subjects with moderate-to-severe chronic non-cancer pain. In this study, 193 subjects received TROXYCA ER for at least 6 months and 105 subjects received TROXYCA ER for approximately 12 months.

Adverse reactions reported in ≥2% of subjects of the 12-month open-label safety study are presented in Table 3.

Table 3. Adverse Drug Reactions Reported in ≥2% of Subjects in the 12-Month Open-Label Safety Study

System Organ Class	TROXYCA ER (N=395)
Adverse Drug Reaction (ADR)	**n (%)**
Gastrointestinal disorders	
Abdominal pain[a]	33 (8.4)
Constipation	84 (21.3)
Diarrhea	36 (9.1)
Dry mouth	9 (2.3)
Nausea	100 (25.3)
Vomiting	55 (13.9)
General disorders and administration site conditions	
Fatigue	36 (9.1)
Edema peripheral	15 (3.8)
Musculoskeletal and connective tissue disorders	
Arthralgia	13 (3.3)
Back pain	25 (6.3)
Muscle spasms	9 (2.3)
Nervous system disorders	
Dizziness	34 (8.6)
Headache	46 (11.6)
Somnolence[b]	38 (9.6)
Tremor	8 (2.0)
Psychiatric disorders	
Depression	13 (3.3)
Insomnia	20 (5.1)
Restlessness	9 (2.3)
Respiratory, thoracic and mediastinal disorders	
Cough	10 (2.5)
Oropharyngeal pain	9 (2.3)
Skin and subcutaneous tissue disorders	
Hyperhidrosis[c]	27 (6.8)
Pruritus[d]	22 (5.6)
Vascular disorders	
Hot flush[e]	17 (4.3)

a. Abdominal pain also includes Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, and Gastrointestinal pain.
b. Somnolence also includes Sedation.
c. Hyperhidrosis also includes Cold sweat.
d. Pruritus also includes Pruritus generalized.
e. Hot flush also includes Flushing.

Less Common Adverse Reactions

The following adverse reactions occurred in patients taking TROXYCA ER in controlled and uncontrolled Phase 3 clinical trials with a frequency of <2%. Adverse reactions are listed in descending order of frequency within System Organ Class.

Table 4. Adverse Drug Reactions Reported in <2% of Subjects in All Phases of the TROXYCA ER Phase 3 Studies

System Organ Class	Adverse Drug Reaction (ADR) Preferred Term
Blood and lymphatic disorders	Anemia, Lymphadenopathy
Cardiac disorders	Tachycardia, Palpitations, Bradycardia
Ear and labyrinth disorders	Vertigo, Tinnitus
Eye disorders	Lacrimation increased
Gastrointestinal disorders	Dyspepsia
General disorders and administration site conditions	Chills, Pain, Influenza like illness, Irritability, Chest pain[a], Pyrexia, Edema, Malaise
Immune system disorders	Drug hypersensitivity[b]
Investigations	Blood pressure increased, Blood testosterone decreased, Blood glucose increased[c], Liver function test abnormal[d]
Metabolism and nutrition disorders	Decreased appetite, Gout
Musculoskeletal and connective tissue disorders	Myalgia, Muscle twitching, Musculoskeletal stiffness, Arthritis
Nervous system disorders	Paresthesia, Lethargy, Disturbance in attention, Migraine, Dysgeusia
Psychiatric disorders	Abnormal dreams, Confusional state, Disorientation, Libido decreased, Drug abuse
Renal and urinary disorders	Dysuria, Hematuria
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea, Bronchitis chronic, Dyspnea, Dysphonia
Skin and subcutaneous tissue disorders	Rash[e], Urticaria
Surgical and medical procedures	Intentional drug misuse

a. Chest pain also includes Chest discomfort and Non-cardiac chest pain.
b. Drug hypersensitivity also includes Hypersensitivity.
c. Blood glucose increased also includes Diabetes mellitus inadequate control.
d. Liver function test abnormal includes Alanine aminotransferase increased and Aspartate aminotransferase increased.
e. Rash also includes Rash pruritic.

6.2 Postmarketing Experience

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

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

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

Anaphylaxis and pharyngeal edema: Anaphylaxis and pharyngeal edema have been reported with ingredients contained in TROXYCA ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

Myocardial ischemia and ventricular fibrillation: Myocardial ischemia and ventricular fibrillation have been reported with oxycodone overdose.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with TROXYCA ER.

Table 5: Clinically Significant Drug Interactions with TROXYCA ER

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of TROXYCA ER and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of TROXYCA ER and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after stable dose of TROXYCA ER is achieved *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of TROXYCA ER until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the TROXYCA ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of TROXYCA ER and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the TROXYCA ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider TROXYCA ER dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of CNS depressants can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Consider dose reduction of one or both drugs. Monitor patients for signs of respiratory depression, sedation, and hypotension *[see Warnings and Precautions (5.2)]*.
Examples	Alcohol, benzodiazepines, and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue TROXYCA ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of TROXYCA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of TROXYCA ER and/or the muscle relaxant, as necessary.

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	The concomitant use of MAOIs can potentiate the effects of oxycodone and can increase the risk of anxiety, confusion, hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when TROXYCA ER is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available data with TROXYCA ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Because plasma naltrexone levels were detectable in some patients administered TROXYCA ER in the clinical trials *[see Clinical Pharmacology (12.3)]*, the naltrexone component of TROXYCA ER may precipitate withdrawal in a fetus due to the immaturity of the fetal blood-brain barrier.

Animal reproduction studies with oral administrations of oxycodone HCl in rats and rabbits during the period of organogenesis at doses equal to or 3-times, respectively, the human dose of 160 mg/day did not reveal evidence of teratogenicity or embryo-fetal toxicity. In several published studies, treatment of pregnant rats with oxycodone at clinically relevant doses and below, resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy can occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or Delivery

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

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone HCl administered during the period of organogenesis up to 16 mg/kg/day and up 25 mg/kg/day, respectively. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity due to oxycodone. The highest doses tested in rats and rabbits were equivalent to approximately 1 and 3 times an adult human dose of 160 mg/day, respectively, on a mg/m^2 basis. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit neurobehavioral effects including altered

stress responses, increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.1-times an adult human dose of 160 mg/day, on a mg/m^2 basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; equivalent to an adult human dose of 160 mg/day, on a mg/m^2 basis).

8.2 Lactation

Risk Summary

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

Clinical Considerations

Monitor infants exposed to TROXYCA ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped or when breastfeeding is stopped. Because plasma naltrexone levels were detectable in some patients administered TROXYCA ER in the clinical trials *[see Clinical Pharmacology (12.3)]*, the naltrexone component of TROXYCA ER may precipitate opioid withdrawal in a breastfed infant.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

8.4 Pediatric Use

The safety and efficacy of TROXYCA ER in patients less than 18 years of age have not been established.

8.5 Geriatric Use

The pharmacokinetics of TROXYCA ER have not been investigated in elderly patients (≥65 years) although such patients were included in clinical studies. Clinical studies with TROXYCA ER did not include sufficient numbers of subjects aged 65 and older to determine if they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease, and use of other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of TROXYCA ER slowly in geriatric patients *[see Warnings and Precautions (5.6)]*.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Since oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Naltrexone is sequestered in the TROXYCA ER capsules and is not intended to be released when TROXYCA ER is used as directed. However, measurable naltrexone plasma concentrations have been observed in some patients in clinical trials with TROXYCA ER *[see Clinical Pharmacology (12.3)]*. An increase in naltrexone AUC in patients with compensated and decompensated liver cirrhosis, compared with subjects with normal liver function, has been reported *[see Clinical Pharmacology (12.3)]*. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Dose initiation of TROXYCA ER should follow a conservative approach in patients with hepatic impairment. In patients with hepatic impairment, there is a potential for differential increase in naltrexone exposure compared to oxycodone exposure. Hence, when administering TROXYCA ER to patients with hepatic impairment, monitor patients closely for signs of central nervous system 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.

8.7 Renal Impairment

Elimination of oxycodone is reported to be impaired in patients with renal impairment.

Although naltrexone is sequestered in the TROXYCA ER formulations, measurable naltrexone plasma concentrations have been observed in some patients in clinical trials with TROXYCA ER *[see Clinical Pharmacology (12.3)]*. Since naltrexone and its primary metabolite are excreted primarily in urine, their plasma concentrations may be increased in patients with renal impairment.

Dose initiation of TROXYCA ER should follow a conservative approach in patients with renal impairment. In patients with renal impairment, there is a potential for differential increase in naltrexone exposure compared to oxycodone exposure. Hence, when administering TROXYCA ER to patients with renal impairment, monitor patients closely for signs of central nervous system 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.

8.8 Sex Differences

There are no clinically significant differences in oxycodone pharmacokinetics following oral administration of TROXYCA ER to males or females; therefore, no specific dosage adjustment is recommended for the initiation or maintenance of TROXYCA ER doses based on the sex of the patient *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TROXYCA ER contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

TROXYCA ER contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. TROXYCA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all persons with substance use disorders. In addition, abuse of opioids can occur in the absence of true addiction.

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

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

Risks Specific to Abuse of TROXYCA ER

TROXYCA ER is for oral use only. Abuse of TROXYCA ER poses a risk of overdose and death. This risk is increased with concurrent abuse of TROXYCA ER with alcohol and other central nervous system depressants. Cutting, breaking, chewing, crushing, or dissolving the pellets in TROXYCA ER and then swallowing, snorting or injecting will result in uncontrolled delivery of the oxycodone and increases the risk of overdose and death. The sequestered naltrexone HCl in TROXYCA ER is intended to have no clinical effect when TROXYCA ER is taken as directed; however, if the capsules are crushed or chewed, up to 100% of the sequestered naltrexone HCl dose could be released, equivalent to an immediate-release (IR) naltrexone HCl oral solution of the same dose. In opioid-tolerant individuals, the absorption of naltrexone HCl may increase the risk of precipitating withdrawal.

Due to the presence of talc as one of the excipients in TROXYCA ER, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Abuse Deterrence Studies

TROXYCA ER is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing.

In Vitro Testing

In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When TROXYCA ER is crushed and mixed in a variety of solvents, both oxycodone HCl and naltrexone HCl are simultaneously extracted.

Clinical Abuse Potential Studies

Two randomized, double-blind active- and placebo-controlled studies were conducted in non-dependent opioid abusers to characterize the abuse potential of oral or intranasal administration of TROXYCA ER following physical manipulation. A third randomized, double-blind, single-dose, placebo and active-controlled study was conducted with IV administration of simulated crushed TROXYCA ER. For these studies, Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking. Response to whether the subject would Take Drug Again was measured on a bipolar 100-point VAS where 0 represents strongest negative response (e.g., 'definitely would not take drug again'), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., 'definitely would take drug again').

The pharmacokinetic profiles of oxycodone HCl and naltrexone HCl were also determined in these abuse potential studies. When TROXYCA ER was crushed and administered orally (40 mg/4.8 mg and 60 mg/7.2 mg doses) or intranasally (30 mg/3.6 mg doses), oxycodone HCl and naltrexone HCl were both absorbed rapidly with median time-to-peak concentration (T_{max}) values of approximately 0.6-1 hour and 0.6 hours, respectively, following oral administration and 1.6 hours and 0.3 hours, respectively, following intranasal administration.

Oral Abuse Potential Study

In this study, 31 non-dependent, recreational opioid abusers received all six treatments by the oral route: crushed 40 mg/4.8 mg TROXYCA ER in solution, crushed 40 mg immediate-release (IR) oxycodone HCl in solution, intact 60 mg/7.2 mg TROXYCA ER, crushed 60 mg/7.2 mg TROXYCA ER in solution, crushed 60 mg IR oxycodone HCl in solution, and placebo. When 40 mg/4.8 mg TROXYCA ER and 60 mg/7.2 mg TROXYCA ER were crushed and taken orally, the geometric mean (SD) values for naltrexone HCl C_{max} were 1074 (1463) pg/mL and 1810 (2450) pg/mL respectively; the AUC_{0-2h} values were 1217 (1471) and 2010 (1839) pg·h/mL, and the AUC_{inf} values were 2877 (2834) pg·h/mL and 4695 (3714) pg·h/mL, respectively.

Oral administration of crushed 40 mg/4.8 mg TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed 40 mg IR oxycodone HCl. Oral administration of crushed 60 mg/7.2 mg TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking E_{max} compared to crushed 60 mg IR oxycodone HCl. The mean and median Take Drug Again E_{max} for crushed 60 mg/7.2 mg TROXYCA ER compared with crushed 60 mg IR oxycodone HCl was numerically lower; however, this finding did not reach statistical significance. The results from this study are summarized in Table 6.

Table 6. Summary Statistics of Abuse Potential Measures of Drug Liking (E_{max}) and Take Drug Again (E_{max}) following Oral Administration

Bipolar VAS Scale (100 point)		Placebo N=31	TROXYCA ER 40 mg/4.8 mg Crushed N=31	IR Oxycodone 40 mg Crushed N=31	TROXYCA ER 60 mg/7.2 mg Intact N=31	TROXYCA ER 60 mg/7.2 mg Crushed N=31	IR Oxycodone 60 mg Crushed N=31
Drug Liking (E_{max})*	Mean (SE)	51.6 (0.68)	69.5 (3.45)	85.6 (2.94)	59.3 (2.75)	74.3 (3.30)	90.0 (2.46)
	Median (range)	51.0 (50,68)	64.0 (50,100)	94.0 (50,100)	51.0 (50,100)	73.0 (50,100)	100.0 (57,100)
Take Drug Again (E_{max})*	Mean (SE)	45.5 (3.47)	56.7 (6.00)	82.9 (3.66)	47.7 (5.12)	71.1 (5.08)	80.6 (4.56)
	Median (range)	50.0 (0,92)	58.0 (0,100)	90.0 (30,100)	50.0 (0,100)	77.0 (0,100)	90.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Among the 31 subjects who received both TROXYCA ER and IR oxycodone by the oral route, 74% (23) and 77% (24) experienced some reduction in Drug Liking E_{max} with crushed 40 mg/4.8 mg TROXYCA ER and crushed 60 mg/7.2 mg TROXYCA ER, respectively, compared to crushed IR oxycodone, while 26% (8) and 23% (7) of subjects had no reduction in Drug Liking E_{max} for crushed 40 mg/4.8 mg TROXYCA ER and crushed 60 mg/7.2 mg TROXYCA ER, respectively, compared to crushed IR oxycodone. With crushed 40 mg/4.8 mg TROXYCA ER, 65% (20) of subjects had at least a 30% reduction and 55% (17) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 40 mg IR oxycodone. With crushed 60 mg/7.2 mg TROXYCA ER, 61% (19) of subjects had at least a 30% reduction and 45% (14) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 60 mg IR oxycodone.

Intranasal Abuse Potential Study
In this study, 27 non-dependent, recreational opioid abusers with experience with intranasal administration of opioids received all four treatments by the intranasal route: crushed 30 mg/3.6 mg TROXYCA ER, crushed 30 mg IR oxycodone HCl, crushed placebo sugar spheres and crushed placebo lactose tablets. Placebo sugar spheres and placebo lactose tablets were weight matched to TROXYCA ER or IR oxycodone HCl. When TROXYCA ER was crushed and taken intranasally, the geometric mean (SD) values for naltrexone HCl C_{max}, AUC_{0-2h}, and AUC_{inf} were 4372 (1409) pg/mL, 5481 (1472) pg·hr/mL, and 10710 (3213) pg·hr/mL, respectively.

Intranasal administration of crushed TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed IR oxycodone HCl (summary statistics for Drug Liking and Take Drug Again in Table 7).

Table 7. Summary Statistics of Abuse Potential Measures for Drug Liking and Take Drug Again with Intranasal Administration of Crushed TROXYCA ER Compared to Crushed IR Oxycodone HCl

VAS Scale (100 point)		Placebo for TROXYCA ER N=27	TROXYCA ER 30 mg/3.6 mg Crushed N=27	Placebo for IR Oxycodone N=27	IR Oxycodone 30 mg Crushed N=27
Drug Liking (E_{max})*	Mean (SE)	51.0 (0.23)	60.3 (2.36)	51.3 (0.65)	93.7 (2.11)
	Median (range)	51.0 (50,56)	55.0 (50,100)	51.0 (50,68)	100.0 (50,100)
Take Drug Again (E_{max})*	Mean (SE)	47.9 (2.92)	58.1 (6.27)	46.5 (3.67)	88.5 (5.18)
	Median (range)	50.0 (0,83)	51.0 (0,100)	50.0 (0,98)	100.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Among 27 subjects who received both TROXYCA ER and IR oxycodone by the intranasal route, 93% (25) experienced some reduction in Drug Liking E_{max} with crushed TROXYCA ER compared to crushed IR oxycodone, while 7% (2) of subjects had no reduction in Drug Liking E_{max} for crushed TROXYCA ER compared to crushed IR oxycodone. With crushed TROXYCA ER 93%

(25) of subjects had at least a 30% reduction in Drug Liking E_{max} and 85% (23) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed IR oxycodone.

Simulated IV Abuse Potential Study
This study in non-dependent recreational opioid abusers compared 20 mg IV oxycodone HCl in combination with 2.4 mg IV naltrexone HCl (to simulate parenteral use of crushed TROXYCA ER) to 20 mg of IV oxycodone HCl and placebo; 29 subjects received all three treatments. These doses were based on the assumption of the complete release of both oxycodone HCl and naltrexone HCl upon crushing TROXYCA ER. Intravenous administration of the combination of oxycodone HCl and naltrexone HCl was associated with statistically significantly lower mean and median Drug Liking and Take Drug Again E_{max} scores (median scores 51 and 50, respectively) compared with oxycodone alone (median scores 97 and 81, respectively). Among 29 subjects, 90% (26) experienced some reduction in E_{max} of Drug Liking with simulated parenteral use of crushed TROXYCA ER compared to IV oxycodone HCl, while 10% (3) of subjects had no reduction in Drug Liking E_{max} for simulated parenteral use of crushed TROXYCA ER compared to IV oxycodone HCl.

Summary
The in vitro and pharmacokinetic data demonstrate that crushing TROXYCA ER pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl. These data along with results from the oral and intranasal human abuse potential studies indicate that TROXYCA ER has properties that are expected to reduce abuse via the oral and intranasal routes. However, abuse of TROXYCA ER by these routes is still possible.

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

A human abuse potential study of intravenous oxycodone HCl and naltrexone HCl to simulate crushed TROXYCA ER demonstrated lower Drug Liking and Take Drug Again E_{max} compared with oxycodone HCl alone. However, it is unknown whether these results with simulated crushed TROXYCA ER predict a reduction in abuse by the IV route until additional postmarketing data are available.

TROXYCA ER contains oxycodone HCl, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. TROXYCA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine).

Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

TROXYCA ER should not be abruptly discontinued *[see Dosage and Administration (2.4)]*. If TROXYCA ER is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

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

10 OVERDOSAGE

Clinical Presentation
Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, noncardiogenic pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

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

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal would be expected to be less than the duration of action of oxycodone in TROXYCA ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. TROXYCA ER will continue to release oxycodone, with systemic exposures of oxycodone for up to 48 hours after administration, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

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

The sequestered naltrexone HCl in TROXYCA ER has no role in the treatment of opioid overdose.

11 DESCRIPTION

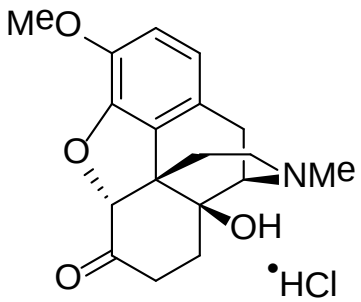
TROXYCA ER extended-release capsules contain pellets of oxycodone HCl with naltrexone HCl at a ratio of 100:12 in each capsule strength for oral administration. The capsule strength describes the amount of oxycodone HCl/naltrexone HCl per capsule. Oxycodone HCl is an opioid agonist and naltrexone HCl is an opioid antagonist at the mu-opioid receptor.

TROXYCA ER extended-release capsules contain the following inactive ingredients common to all strengths: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, hydroxypropyl cellulose, polyethylene glycol, dibutyl sebacate, sodium lauryl sulfate, diethyl phthalate, magnesium stearate, methacrylic acid copolymer, and ascorbic acid. Each TROXYCA ER capsule (as a component of the capsule shell) also contains gelatin, titanium dioxide, E172 Black Iron Oxide, E172 Yellow Iron Oxide, and black ink.

The 10 mg/1.2 mg capsule does not contain additional excipient other than those listed above.
The 20 mg/2.4 mg capsule also contains FD&C Red #3, FD&C Blue #1, white ink.
The 30 mg/3.6 mg capsule also contains FD&C Blue #1, FD&C Red #3.
The 40 mg/4.8 mg capsule also contains FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6.
The 60 mg/7.2 mg capsule also contains FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6.
The 80 mg/9.6 mg capsule also contains FD&C Blue #1, FD&C Red #3, FD&C Yellow #6.

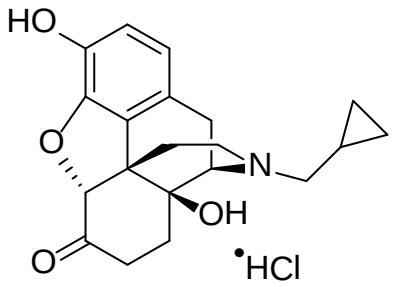
Oxycodone Hydrochloride
The chemical name of oxycodone HCl is 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. The empirical formula is $C_{18}H_{21}NO_4$•HCl and its molecular weight is 351.82.

Oxycodone HCl is a white to off-white, fine powder. It has a solubility of 0.20 g/mL at pH 6. Its structural formula is:



Naltrexone Hydrochloride
The chemical name of naltrexone HCl is (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. The empirical formula is $C_{20}H_{23}NO_4$•HCl and its molecular weight is 377.86.

Naltrexone HCl is a white to slightly off-white powder that is soluble in water. Its structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Naltrexone Hydrochloride
Naltrexone is an opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding at mu-opioid receptors.

12.2 Pharmacodynamics

Effects on the Central Nervous System
Oxycodone produces respiratory depression by direct action on brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

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

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

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

Use caution in hypovolemic patients, such as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

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

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

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

Concentration–Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.3)]*.

Concentration–Adverse Reaction Relationships
There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

The dose of TROXYCA ER must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients *[see Dosage and Administration (2.1)]*.

12.3 Pharmacokinetics

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

Chewing, crushing or dissolving the pellets within the TROXYCA ER capsules impairs the extended-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone as well as a potentially complete release of sequestered naltrexone.

Oxycodone Pharmacokinetics
Oxycodone is a semi-synthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these is mediated by the mu-opioid receptor and involves the central nervous system and organs composed of smooth muscle.

Absorption
In humans, about 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic metabolism of oxycodone. Dose proportionality of oxycodone has been established using IR oxycodone 5, 15 and 30 mg tablets based on extent of absorption (AUC).

Following oral administration of TROXYCA ER capsules, oxycodone T_{max} is delayed to approximately 12 hours post dose (range, 8-16 h), AUC is equivalent and C_{max} is reduced by approximately 67% when compared with IR oxycodone tablets. It takes approximately 18 to 24 hours to reach steady-state plasma concentrations of oxycodone with IR oxycodone. With TROXYCA ER steady state was reached within 48 h. Compared to Day 1, oxycodone C_{max} increased by 86% and AUC_{0-24} increased by 168% at steady state on Day 5. The half-life after single dose is approximately 7 hours and does not change after multiple doses.

An analysis of pharmacokinetic results from Phase 1 single-dose studies with TROXYCA ER capsules 20 mg/2.4 mg up to 80 mg/9.6 mg showed that oxycodone AUC and C_{max} increased in a dose proportional manner. Based on the prescribed daily doses in patients in the Phase 3 studies, the mean steady-state concentrations of oxycodone for 10-40 mg, >40-80 mg, >80-120 mg, and >120 mg daily dose groups were 15 ng/mL, 35 ng/mL, 60 ng/mL, and 83 ng/mL, respectively.

After administration of crushed TROXYCA ER, the peak plasma levels of oxycodone occurred at 0.6-1.0 hours orally and 1.6 hours intranasally.

Food Effect: When a single dose of TROXYCA ER capsules are administered in fasted state or after a high-fat meal, or when the contents of TROXYCA ER capsules are sprinkled on one tablespoon of applesauce and administered in a fasted state, oxycodone pharmacokinetics are unaffected with similar AUC, C_{max}, and T_{max} values *[see Dosage and Administration (2.5)]*.

Distribution
Following intravenous administration, the volume of distribution (Vss) for oxycodone is 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 is about 45%. Oxycodone has been found to be excreted in breast milk *[see Use in Specific Populations (8.2]*.

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

Metabolism
In humans, oxycodone is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. CYP3A-mediated N-demethylation to an inactive metabolite from noroxycodone is the principal metabolic pathway of oxycodone in humans. CYP2D6-mediated *O*-demethylation to an active metabolite oxymorphone is a minor metabolic pathway. Oxymorphone is present in the plasma only in low concentrations

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 ≤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 IR oxycodone is 3.5 to 4 hours. Following oral administration of TROXYCA ER 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 capsules approximately 12 hours apart.

Specific Populations

Elderly (≥65 years)
The effects of age on the pharmacokinetics of TROXYCA ER have not been investigated in a specific study in elderly patients (≥65 years). The safety and efficacy studies with TROXYCA ER did not include sufficient numbers of subjects aged 65 and older. The median age in these studies was 54 years and there were no significant differences in oxycodone concentrations between patients <54 years of age and patients ≥54 years of age. Population pharmacokinetic studies conducted with IR oxycodone indicated that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65.

Sex
The effects of gender on the pharmacokinetics of TROXYCA ER have not been investigated in a specific study. In analyses of oxycodone pharmacokinetic data from studies in healthy volunteers and in patients there was no clinically significant difference observed between males and females.

Hepatic Impairment
The effect of hepatic impairment on oxycodone pharmacokinetics following TROXYCA ER administration has not been investigated. However, since oxycodone is extensively metabolized in the liver, its clearance is expected to decrease in patients with hepatic impairment *[see Use in Specific Populations (8.6)]*.

Renal Impairment
Elimination of oxycodone is reported to be impaired in patients with renal impairment. The mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance *[see Use in Specific Populations (8.7)]*.

Alcohol Interaction
Concomitant administration of TROXYCA ER 20 mg/ 2.4 mg with 20% alcohol did not affect C_{max} or AUC of oxycodone. With concomitant administration of 40% alcohol and TROXYCA ER 20 mg/2.4 mg there was an average 37% increase in C_{max} and 13% increase in AUC of oxycodone compared with TROXYCA ER administered with water. Out of 17 subjects, one subject had 1.7 fold and 5.4 fold increase in C_{max} following administration of TROXYCA ER with 20% alcohol and 40% alcohol, respectively, compared to TROXYCA ER administered with water. The corresponding increases in AUC in this subject were 1.2 fold and 3.8 fold with 20% and 40 % alcohol treatments, respectively, compared to water. There was no suggestion of overexposure to oxycodone in this subject, as oxycodone exposures when TROXYCA ER was administered with 20% or 40% ethanol were within the range of exposures seen in other subjects.

Drug-Drug Interactions
While no specific drug interaction studies have been performed with TROXYCA ER, an interaction with inhibitors and inducers of the CYP3A4 enzyme is expected based on the metabolism of oxycodone predominantly by CYP3A4 *[see Drug Interactions (7)]*.

CYP2D6 Inhibitors
Oxycodone is metabolized, in part, to oxymorphone via the cytochrome p450 isoenzyme CYP2D6 *[see Drug Interactions (7)]*.

Naltrexone Pharmacokinetics
Naltrexone blocks the effects of opioids by competitive binding at mu-opioid receptors. Naltrexone has few, if any intrinsic actions besides its opioid-blocking properties. However, it does produce some pupillary constriction by an unknown mechanism. Naltrexone, administered alone, is not associated with the development of tolerance or dependence, but it will precipitate withdrawal symptoms in subjects physically dependent on opioids.

Absorption
When TROXYCA ER capsules are administered in a fasted state or after a high-fat meal or when the contents of TROXYCA ER capsules are sprinkled on applesauce and administered in fasted state, naltrexone plasma concentrations remain undetectable (below the limit of quantitation, 4 pg/mL) suggesting that administration of TROXYCA ER capsules with food or sprinkling of the pellets on applesauce does not affect sequestration of naltrexone. The maximum plasma 6-β-naltrexol concentration was 30 pg/mL, observed at 120 h post dose following TROXYCA ER after a high-fat meal.

Following single-dose administration of intact TROXYCA ER in Phase 1 studies, naltrexone was undetected (limit of quantitation, 4 pg/mL). 6-β-naltrexol (limit of quantitation, 4 pg/mL) was observed in 20 out of 37 subjects with a median (range) of 7.8 (4.1-45.4) pg/mL.

Naltrexone plasma concentrations were undetected in the majority (78%) of the samples (n=2407) collected from patients in the Phase 3 studies. In the samples with measurable naltrexone concentrations, the median (range) was 11.2 (4.1-1090) pg/mL. At least one measureable naltrexone level was observed in 249 subjects (34%) out of 725 subjects. 6-β-naltrexol plasma concentrations were undetected in 40% of the samples (n=2544) collected from patients in the Phase 3 studies. In the samples with measurable 6-β-naltrexol concentrations, the median (range) was 42.5 (4.1-7320) pg/mL. At least one measureable 6-β-naltrexol level was observed in 536 subjects (73%) out of 735 subjects.

Upon oral administration of crushed TROXYCA ER, 100% of the sequestered naltrexone is released, with bioavailability equivalent to immediate-release naltrexone in solution at the same dose. Although well absorbed orally, naltrexone is subject to significant first-pass metabolism, with mean absolute oral bioavailability estimates of about 9.1% and 8.4% following orally administered crushed TROXYCA ER 40 mg/4.8 mg and 60 mg/7.2 mg doses, respectively. The absolute intranasal bioavailability of naltrexone was about 41.6% following intranasally administered crushed TROXYCA ER 30 mg/3.6 mg, and was higher compared with oral bioavailability due to avoiding hepatic and intestinal first-pass metabolism with the intranasal route. After administration of crushed TROXYCA ER, the peak plasma levels of naltrexone occurred at 0.55 hours orally and 0.32 hours intranasally.

Following oral administration of naltrexone immediate-release tablets, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. The rate and extent of absorption (C_{max} and AUC, respectively) of naltrexone immediate-release tablets have been shown to increase in a dose proportional manner following oral administration of naltrexone 50 mg tablets as 50, 100 and 200 mg doses. The bioavailability of naltrexone given as 50 mg tablets was similar to that of the same dose given as a 10 mg/mL solution.

Distribution
The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters. In vitro tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

Elimination
In humans, naltrexone is highly metabolized. Naltrexone metabolites are excreted via the kidney.

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

Excretion
In humans, naltrexone is excreted primarily in the urine as conjugates of naltrexone and 6ß-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 6ß-naltrexol ranges from 230 to 369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6ß-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 6ß-naltrexol are 4 hours and 13 hours, respectively.

Special Populations

Hepatic Impairment
Since naltrexone is extensively metabolized, its clearance may decrease in hepatic failure patients. An increase in naltrexone AUC of approximately 5-and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. This study suggested increased bioavailability of naltrexone in liver cirrhosis, consistent with lesser metabolism of naltrexone to 6ß-naltrexol, and appears to be related to the severity of liver disease.

Renal Impairment
Adequate studies of naltrexone tablets in patients with renal impairment have not been conducted. Since naltrexone and its primary metabolite are excreted primarily in urine, plasma concentrations of naltrexone may increase in patients with renal impairment *[see Use in Specific Populations (8.7)]*.

Drug-Drug Interactions
No specific drug interaction studies have been performed with TROXYCA ER. Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of naltrexone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies in animals to evaluate the carcinogenic potential of TROXYCA ER or oxycodone have not been conducted.

Mutagenesis
Oxycodone HCl was genotoxic in an in vitro mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an in vitro bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

Impairment of Fertility
Fertility studies have not been performed in animals to evaluate the potential impact on fertility of TROXYCA ER or oxycodone.

14 CLINICAL STUDIES

The analgesic efficacy of TROXYCA ER has been evaluated in one randomized, double-blind, placebo-controlled clinical trial in patients with moderate-to-severe chronic low back pain. This study utilized an enriched-enrollment, randomized-withdrawal design and was conducted in a population consisting of both opioid-experienced and opioid-naïve subjects. Subjects were titrated to effect with TROXYCA ER in the open-label period, which was followed by a 12-week double-blind treatment period. Total daily doses of the oxycodone in TROXYCA ER ranged from 20 mg to 160 mg administered in two equal doses approximately 12 hours apart. Subjects with controlled pain (defined as pain intensity numerical rating scale [NRS] ≤4) were randomized into the 12-week double-blind treatment period to either continue TROXYCA ER or be switched to placebo. Subjects randomized to placebo were given a blinded taper of TROXYCA ER according to a pre-specified schedule to prevent opioid withdrawal. Rescue medication (up to 3 grams per day of acetaminophen) was allowed throughout the study to treat episodes of breakthrough pain. Immediate-release oxycodone HCl (as a single ingredient product) was also allowed during the first 3 weeks of the open-label period to manage the initial conversion from prior therapy.

A total of 410 subjects entered the open-label titration period and 281 were successfully titrated onto TROXYCA ER and randomized into the double-blind treatment period: 134 to placebo and 147 to TROXYCA ER. Of these, 42.5% of subjects were previously treated with an opioid.

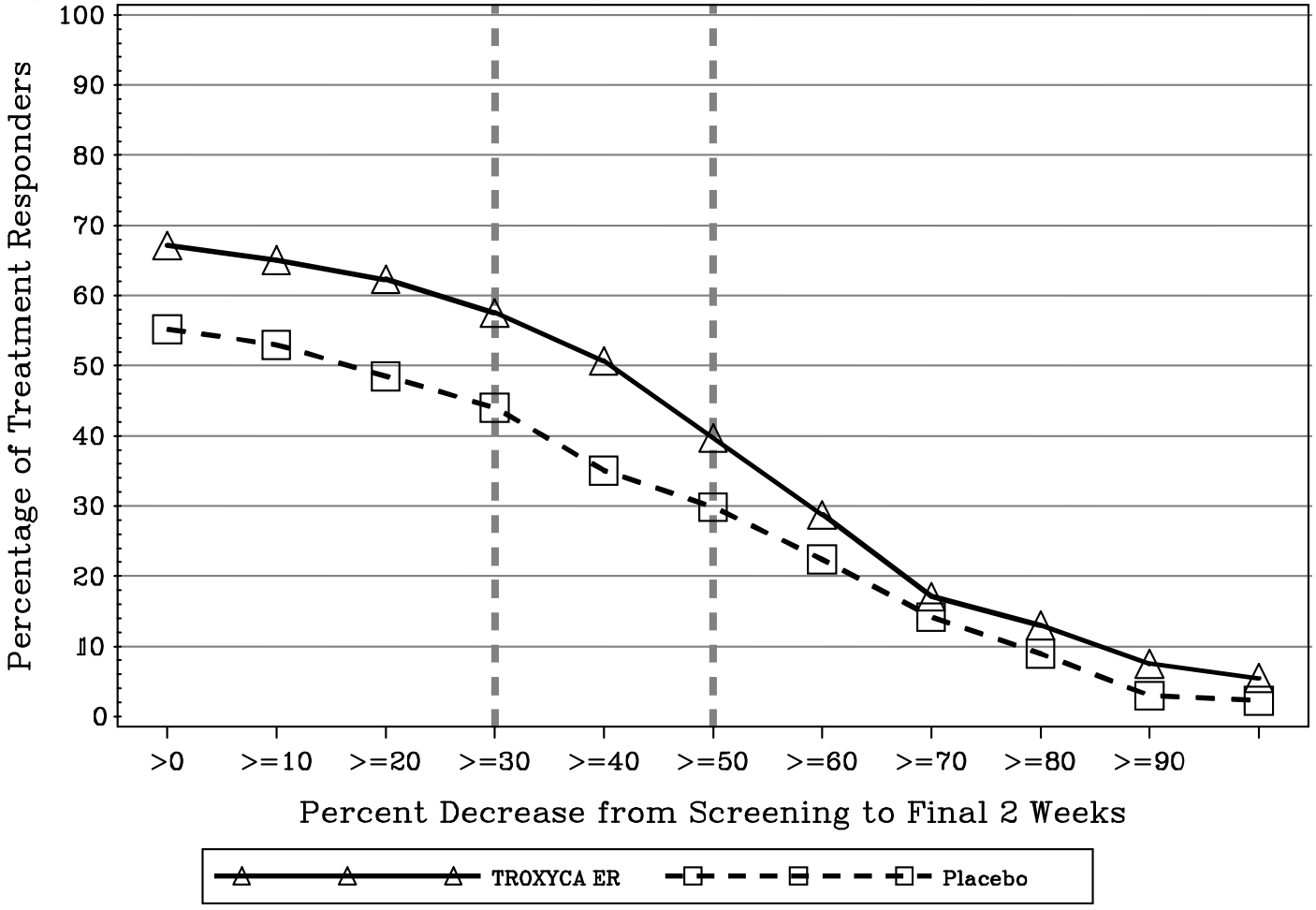
In the open-label titration period, 57% of subjects were female and 43% were male with the majority of subjects being less than 65 years of age (89%) and white (73%). Overall, in the double-blind treatment period, 56% of subjects were female and 44% were male with a median age of 51 years and the majority (73%) of subjects being white. Subject demographics were similar between placebo and TROXYCA ER groups.

A total of 188 (67%) subjects completed the double-blind treatment period, including 107 (73%) TROXYCA ER subjects and 81 (60%) placebo subjects. More subjects in the placebo group discontinued due to lack of efficacy (12%) compared to TROXYCA ER (3%), and more subjects discontinued due to adverse events in the TROXYCA ER group (10%) compared to placebo (7%). Subjects discontinued from the open-label titration period for the following reasons: adverse events (n=57), protocol violations (n=7), lost to follow-up (n=10), did not meet entrance criteria (n=41), no longer willing to participate (n=11), and other (n=3). Subjects discontinued from the double-blind treatment period from the placebo group for the following reasons: insufficient clinical response (n=16), adverse event (n=9), protocol violation (n=8), lost to follow-up (n=3), no longer willing to participate (n=11), and other (n=6) and

from the TROXYCA ER group for the following reasons: insufficient clinical response (n=4), adverse event (n=14), protocol violation (n=9), lost to follow-up (n=6), no longer willing to participate (n=6), and other (n=1).

The mean change in the weekly average pain intensity NRS scores from randomization baseline to the average of Weeks 11 and 12 was statistically significantly superior for those treated with TROXYCA ER compared to placebo. The percentage of patients (responders) in each group who demonstrated improvement in their final 2 weeks, as compared with screening is shown in Figure 1. The figure is cumulative, so that patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were classified as non-responders. A higher percentage of subjects receiving TROXYCA ER, compared to placebo, had a ≥30% decrease in their weekly average NRS-pain intensity scores from Screening to Weeks 11 and 12 of the double-blind treatment period (58% versus 44% for TROXYCA ER and placebo, respectively), while, 40% of subjects receiving TROXYCA ER and 30% of subjects receiving placebo had a 50% decrease.

Figure 1. Percent Reduction Profiles for Weekly Average Daily Pain Scores from Screening to Final 2 Weeks



16 HOW SUPPLIED/STORAGE AND HANDLING

Oxycodone HCl / naltrexone HCl	TROXYCA ER 10 mg/1.2 mg	TROXYCA ER 20 mg/2.4 mg	TROXYCA ER 30 mg/3.6 mg	TROXYCA ER 40 mg/4.8 mg	TROXYCA ER 60 mg/7.2 mg	TROXYCA ER 80 mg/9.6 mg
Extended-Release Capsule Description	Two-toned hard gelatin capsule, silver opaque body, yellow opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, violet opaque cap, black print on body and white print on cap	Two-toned hard gelatin capsule, silver opaque body, fuchsia opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, olive green opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, green opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, brick red opaque cap, black print
NDC #	60793-537-01	60793-531-01	60793-535-01	60793-532-01	60793-533-01	60793-536-01

Bottle count for each of these strengths is 100.
Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F).
Dispense in tight (USP), light-resistant, child-resistant containers.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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

Life-threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting TROXYCA ER or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion
Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store TROXYCA ER securely and to dispose of unused TROXYCA ER by flushing the capsules down the toilet.

Interactions with Alcohol and Other CNS Depressants
Inform patients that potentially serious additive effects may occur if TROXYCA ER is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a healthcare provider *[see Warnings and Precautions (5.5)]*.

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

Adrenal Insufficiency
Inform patients that TROXYCA ER could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.7)]*.

Important Administration Instructions
Instruct patients how to properly take TROXYCA ER, including the following:

- Swallow TROXYCA ER capsules whole or sprinkle the capsule contents on applesauce and then swallow immediately without chewing *[see Dosage and Administration (2.1)]*.

- Do not crush, chew, or dissolve the pellets contained in the capsules due to a risk of fatal oxycodone overdose or naltrexone precipitated withdrawal symptoms in opioid-dependent individuals *[see Dosage and Administration (2.1)]*.
- Use TROXYCA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) *[see Warnings and Precautions (5.2)]*.
- Do not discontinue TROXYCA ER without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.4)]*.

Hypotension
Inform patients that TROXYCA ER may cause hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.8)]*.

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

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of TROXYCA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Embryofetal Toxicity
Inform female patients of reproductive potential that TROXYCA ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

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

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

Driving or Operating Heavy Machinery
Inform patients that TROXYCA ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.13)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Disposal of Unused TROXYCA ER
Advise patients to flush the unused capsules down the toilet when TROXYCA ER is no longer needed.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

LAB-0714-1.10

Medication Guide
TROXYCA® ER (TROKS' ih-ka ee' ahr)
(oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules, CII

TROXYCA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about TROXYCA ER:

- **Get emergency help right away if you take too much TROXYCA ER (overdose).** When you first start taking TROXYCA ER, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Never give anyone your TROXYCA ER. They could die from taking it. Store TROXYCA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away TROXYCA ER is against the law.

Do not take TROXYCA ER if you have:

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

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

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of TROXYCA ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with TROXYCA ER. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking TROXYCA ER with certain other medicines can cause serious side effects that could lead to death.

When taking TROXYCA ER:

- Do not change your dose. Take TROXYCA ER exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours, at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow TROXYCA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject TROXYCA ER because this may cause you to overdose and die.
- Do not give TROXYCA ER through a nasogastric tube or gastric tube (stomach tube).
- If you cannot swallow TROXYCA ER capsules, see the detailed Instructions for Use.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking TROXYCA ER without talking to your healthcare provider.**
- After you stop taking TROXYCA ER, flush any unused capsules down the toilet.

While taking TROXYCA ER DO NOT:

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

The possible side effects of TROXYCA ER are:

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

Get emergency medical help if you have:

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

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

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LAB-0715-1.0

Instructions For Use
TROXYCA® ER (TROKS' ih-ka ee' ahr)
(oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules, CII

- If you cannot swallow TROXYCA ER capsules whole, tell your healthcare provider. If your healthcare provider tells you that you can take TROXYCA ER by sprinkling the capsule contents on applesauce, follow these steps:

TROXYCA ER can be opened and the contents inside the capsule can be sprinkled on applesauce, as follows:

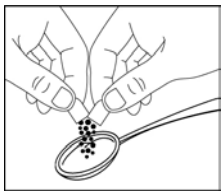
Figure 1

- Open the TROXYCA ER capsule and sprinkle the contents over about one tablespoon of applesauce (See Figure 1).

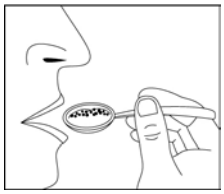
Figure 2

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

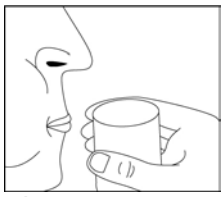
Figure 3

- Rinse your mouth to make sure you have swallowed all of the capsule contents. Do not chew the capsule contents (See Figure 3).

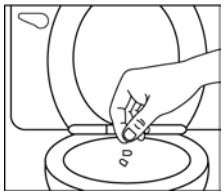
Figure 4

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

- Do not give TROXYCA ER through a nasogastric tube or gastric tube (stomach tube).

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