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

ROXYBOND (oxycodone hydrochloride) tablets, for oral use, CII
Initial U.S. Approval: 1950

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF ROXYBOND
See full prescribing information for complete boxed warning.

- **ROXYBOND exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of ROXYBOND are essential. (5.2)**
- **Accidental ingestion of ROXYBOND, especially by children, can result in a fatal overdose of oxycodone. (5.2)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.3, 7)**
- **If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.4)**
- **Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.5)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.6, 7, 12.3)**

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

Boxed Warning	12/2023
Indications and Usage (1)	12/2023
Dosage and Administration (2.1, 2.3, 2.4)	12/2023
Warnings and Precautions (5.7)	12/2023

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

ROXYBOND is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration (5.1), reserve ROXYBOND for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):

- Have not been tolerated or are not expected to be tolerated,
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

ROXYBOND should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

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

- ROXYBOND should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of ROXYBOND for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with ROXYBOND. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both with initiating and renewing treatment with ROXYBOND. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.2, 5.3).
- Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of ROXYBOND. (2.3, 2.4)
- Do not abruptly discontinue ROXYBOND in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.4, 5.14, 9.3)

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

Tablets: 5 mg, 15 mg, 30 mg (3)

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

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

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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation. (5.7)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of ROXYBOND in patients with circulatory shock. (5.10)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ROXYBOND in patients with impaired consciousness or coma. (5.11)

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

Most common adverse reactions (≥3%): nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Protega Pharmaceuticals Inc. at 1-844-798-3610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue ROXYBOND if serotonin syndrome is suspected. (7)

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- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with ROXYBOND because they may reduce analgesic effect of ROXYBOND or precipitate withdrawal symptoms. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of morphine. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

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

Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2024

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF ROXYBOND

Addiction, Abuse, and Misuse

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

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of ROXYBOND, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of ROXYBOND are essential *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

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

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of ROXYBOND and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.3), Drug Interactions (7)].*

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.5)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of ROXYBOND with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Regularly evaluate patients receiving ROXYBOND and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.6), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

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1 INDICATIONS AND USAGE

ROXYBOND is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, which can occur any dosage or duration *[see Warnings and Precautions (5.1)]*, reserve ROXYBOND for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):

- Have not been tolerated or are not expected to be tolerated,
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

ROXYBOND should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- ROXYBOND should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of ROXYBOND for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks *[see Warnings and Precautions (5)]*.

- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with ROXYBOND. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5.2)]*.

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2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with ROXYBOND *[see Warnings and Precautions (5.2)]*.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosage

Use of ROXYBOND as the First Opioid Analgesic

Initiate treatment with ROXYBOND in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of ROXYBOND.

Although it is not possible to list every condition that is important to the selection of the initial dose of ROXYBOND, attention should be given to: 1) the daily dose, potency, and characteristics of any prior opioid 2) the reliability of any relative potency estimate used to calculate the dose of oxycodone needed, 3) the degree of opioid tolerance, 4) the general condition and medical status of the patient, and 5) the balance between pain control and adverse experiences.

Conversion from Other Opioids to ROXYBOND

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of ROXYBOND. It is safer to underestimate a patient's 24-hour ROXYBOND dosage than to overestimate the 24-hour ROXYBOND dosage and manage an adverse reaction due to overdose. If a patient has been receiving opioid-containing medications prior to taking ROXYBOND, the potency of the prior opioid relative to oxycodone should be factored into the selection of the total daily dose (TDD) of oxycodone.

In converting patients from other opioids to ROXYBOND, close observation and adjustment of dosage based upon the patient's response to ROXYBOND is imperative. Administration of supplemental analgesia for breakthrough or incident pain and titration of the TDD of ROXYBOND may be necessary, especially in patients who have disease states that are changing rapidly.

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Conversion From Fixed-Ratio Opioid/Acetaminophen, Opioid/Aspirin, or Opioid/Nonsteroidal Combination Drugs

When converting patients from fixed ratio opioid/non-opioid drug regimens, a decision should be made whether or not to continue the non-opioid analgesic. If a decision is made to discontinue the use of non-opioid analgesic, it may be necessary to titrate the dose of ROXYBOND in response to the level of analgesia and adverse effects afforded by the dosing regimen. If the non-opioid regimen is continued as a separate single entity agent, the starting dose of ROXYBOND should be based upon the most recent dose of opioid as a baseline for further titration of oxycodone. Incremental increases should be gauged according to side effects to an acceptable level of analgesia.

Conversion from ROXYBOND to Extended-Release Oxycodone

The relative bioavailability of ROXYBOND compared to extended-release oxycodone products is unknown, so conversion to extended-release oxycodone may lead to increased risk of excessive sedation and respiratory depression.

Conversion from Oxycodone Immediate-Release Tablets

Oxycodone pharmacokinetics are similar for ROXYBOND and oxycodone immediate-release tablets. Patients can be converted from oxycodone immediate-release to the same dose and dosing regimen of ROXYBOND.

2.4 Titration and Maintenance of Therapy

Individually titrate ROXYBOND to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving ROXYBOND to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.14)]*. 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.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the ROXYBOND dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.5 Safe Reduction or Discontinuation of ROXYBOND

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

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking ROXYBOND, there are a variety of factors that should be considered, including the total daily dose of opioid (including ROXYBOND) the patient has been taking, the duration of

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treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

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

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

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

3 DOSAGE FORMS AND STRENGTHS

ROXYBOND (oxycodone hydrochloride) tablets, 5 mg, 15 mg and 30 mg with the following characteristics:

Strength	Tablet Shape	Tablet Color	Ink-Print on Tablet Side 1	Ink-Print on Tablet Side 2
5 mg	Round coated tablets	White	IDT/O 5	None
15 mg		Green	IDT/O 15	None
30 mg		Blue	IDT/O 30	None

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4 CONTRAINDICATIONS

ROXYBOND 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 or hypercarbia *[see Warnings and Precautions (5.8)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Known hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

ROXYBOND contains oxycodone, a Schedule II controlled substance. As an opioid, ROXYBOND exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ROXYBOND. Addiction can occur at recommended dosages, when taken as directed, and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ROXYBOND, and reassess all patients receiving ROXYBOND for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ROXYBOND but use in such patients necessitates intensive counseling about the risks and proper use of ROXYBOND along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing ROXYBOND. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and on the proper disposal of unused drugs. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid 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.

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

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

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize on the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.4)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing the treatment with ROXYBOND. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone. *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

5.3 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ROXYBOND with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ROXYBOND is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate dangerous machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

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

5.5 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.

- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.

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- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.

- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

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

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

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

5.7 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)]*. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) [*see Dosage and Administration (2.5), Warnings and Precautions (5.14)*].

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

The use of ROXYBOND 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: ROXYBOND-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 ROXYBOND *[see Warnings and Precautions (5.2)]*.

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

Regularly evaluate patients, particularly when initiating and titrating ROXYBOND and when ROXYBOND is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.3)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.10 Severe Hypotension

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

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

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ROXYBOND may reduce the respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such

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patients for signs of sedation and respiratory depression, particularly when initiating therapy with ROXYBOND.

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

5.12 Risks of Use in Patients with Gastrointestinal Conditions

ROXYBOND is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. The oxycodone in ROXYBOND may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in ROXYBOND may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during ROXYBOND therapy.

5.14 Withdrawal

Do not abruptly discontinue ROXYBOND in a patient physically dependent on opioids. When discontinuing ROXYBOND in a physically-dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.4), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including ROXYBOND. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

5.15 Risks of Driving and Operating Machinery

ROXYBOND 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 ROXYBOND and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are described or are described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*

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

6.1 Clinical 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Oxycodone hydrochloride tablets have been evaluated in open label clinical trials in patients with cancer and nonmalignant pain. Oxycodone hydrochloride tablets are associated with adverse experiences similar to those seen with other opioids.

Serious adverse reactions that may be associated with ROXYBOND therapy include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock.

The common adverse reactions seen on initiation of therapy with oxycodone hydrochloride tablets are dose related and are opioid-related adverse reactions. The most frequent of these included nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. The frequency of these reactions depended on several factors, including clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual.

In all patients for whom dosing information was available (n=191) from the open-label and double-blind studies involving oxycodone hydrochloride tablets, the following adverse events were recorded in oxycodone hydrochloride treated patients with an incidence ≥ 3%. In descending order of frequency they were: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.

Other less frequently observed adverse reactions from opioid analgesics, including oxycodone hydrochloride tablets included:

Blood and lymphatic system disorders: anemia, leukopenia

Cardiac disorders: cardiac failure, palpitation, tachycardia

Gastrointestinal disorders: abdominal pain, dry mouth, diarrhea, dyspepsia, dysphagia, glossitis, nausea, vomiting

General disorders and administration site conditions: chills, edema, edema peripheral, pain, pyrexia

Immune system disorders: hypersensitivity

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Infections and infestations: bronchitis, gingivitis, infection, pharyngitis, rhinitis, sepsis, sinusitis, urinary tract infection

Injury, poisoning, and procedural complications: injury

Metabolism and nutritional disorders: decreased appetite, gout, hyperglycemia

Musculoskeletal and connective tissue disorders: arthralgia, arthritis, back pain, bone pain, myalgia, neck pain, pathological fracture

Nervous system disorders: hypertonia, hypoesthesia, migraine, neuralgia, tremor, vasodilation

Psychiatric disorders: agitation, anxiety, confusional state, nervousness, personality disorder

Respiratory, thoracic, and mediastinal disorders: cough, dyspnea, epistaxis, laryngospasm, lung disorder

Skin and subcutaneous tissue disorders: photosensitivity reaction, rash, hyperhidrosis, urticaria

Vascular disorders: thrombophlebitis, hemorrhage, hypotension, vasodilation

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.

General disorders and administrative site disorders: drug withdrawal syndrome neonatal *[see Warnings and Precautions (5.4)]*

Respiratory, thoracic, and mediastinal disorders: pharyngeal edema

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs *[see Drug Interactions (7)]*.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use *[see Warnings and Precautions (5.9)]*.

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in ROXYBOND *[see Contraindications (4)]*.

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

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

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

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with ROXYBOND.

Table 1. Clinically Significant Drug Interactions with ROXYBOND

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of ROXYBOND 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 ROXYBOND and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of ROXYBOND is achieved *[see Warnings and Precautions (5.6)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of ROXYBOND until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the ROXYBOND dosage until stable drug effects are achieved. Evaluate 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 ROXYBOND and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.6, 5.14)]*. 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.

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Table 1. Clinically Significant Drug Interactions with ROXYBOND	
Intervention	If concomitant use is necessary, consider increasing the ROXYBOND dosage until stable drug effects are achieved. Evaluate patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ROXYBOND dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death *[see Warnings and Precautions (5.3)]*.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2*, 5.3*)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Adverse Reactions (6.2)]*.
Intervention:	If concomitant use is warranted, frequently reevaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue ROXYBOND 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 affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*.
Intervention:	The use of ROXYBOND is not recommended for patients taking MAOIs or within

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Table 1. Clinically Significant Drug Interactions with ROXYBOND	
	14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Examples:	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of ROXYBOND and/or may precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of ROXYBOND and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2*, 5.3*)]*.
Examples:	Cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant risk of anticholinergic drugs may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when ROXYBOND is used concurrently with anticholinergic drugs.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4), Clinical Considerations]*. There are reports of respiratory depression when oxycodone is used during labor and delivery *[see Clinical Considerations]*. There are no available data with ROXYBOND in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Animal reproduction studies with oral administrations of oxycodone hydrochloride in rats and rabbits during the period of organogenesis, at doses 2.6 and 8.1 times, respectively, the human dose of 60 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 risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity, and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, 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 (5.4)]*.

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. ROXYBOND is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including ROXYBOND, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

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Data

Human Data

Limited published data from case-control and observational studies on oxycodone use during pregnancy are inconsistent in their findings. Although some studies reported an increased risk of congenital malformations, there was no consistent pattern of malformations noted. In addition, multiple similar studies reported no association. Methodological limitations of these studies, including small sample size, recall bias, lack of information regarding dose and timing of exposure and concomitant use of other medications, preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of oxycodone in pregnancy.

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone hydrochloride administered during the period of organogenesis up to 16 mg/kg/day and up to 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 2.6 and 8.1 times an adult human dose of 60 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; 0.3-times an adult human dose of 60 mg/day, on a mg/m^2 basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human dose of 60 mg/day, on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Available data from lactation studies indicate that oxycodone is present in breastmilk and that doses of less than 60 mg/day of the immediate-release formulation are unlikely to result in clinically relevant exposures in breastfed infants. A pharmacokinetics study utilizing opportunistic sampling of 76 lactating women receiving oxycodone immediate-release products for postpartum pain management showed that oxycodone concentrates in breastmilk with an average milk to plasma ratio of 3.2. The relative infant dose was low, approximately 1.3% of a weight-adjusted maternal dose (*see Data*).

In the same study, among the 70 infants exposed to oxycodone in breastmilk, no adverse events were attributed to oxycodone. However, based on known adverse effects in adults, infants should be monitored for signs of excess sedation and respiratory depression (*see Clinical Considerations*). There are no data on the effects of the oxycodone on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ROXYBOND and any potential adverse effects on the breastfed infant from ROXYBOND or from the underlying maternal condition.

Clinical Considerations

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

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Data

Oxycodone concentration data from 76 lactating women receiving immediate-release oxycodone products for postpartum pain management, and 28 infants exposed to oxycodone in breastmilk showed that following a median (range) dose of oxycodone in mothers of 9.2 (5-10) mg/dose or 33.0 (5.4-59.3) mg/day, oxycodone concentrated in breastmilk with a median (range) milk to plasma ratio of 3.2 (1.2-5.3). However, when using maternal breastmilk data to estimate the daily and relative infant dose, the infant dose was 0.006 mg/kg/day, which is 1.3% of a weight-adjusted maternal dose of 10 mg every 6 hours. These estimates based on maternal breastmilk concentrations were corroborated by the observed infant concentrations, of which over 75% (19/25) were below the limit of quantification. Among the 6 infants with quantifiable concentration, the median (range) concentration was 0.2 ng/mL (0.1-0.7). These concentrations are 100 to 1000 times lower than concentrations observed in other studies after infants received oxycodone at 0.1 mg/kg/dose (~20-200 ng/mL).

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

The safety and efficacy of ROXYBOND in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of oxycodone hydrochloride, 20.8% (112/538) were 65 and over, while 7.2% (39/538) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 and of concomitant disease or 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 ROXYBOND slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)]*.

Oxycodone 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

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likely to have decreased renal function, care should be taken in dose selection, and it may be useful to regularly evaluate renal function.

8.6 Hepatic Impairment

Because oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Initiate therapy in these patients with a lower than usual dosage of ROXYBOND and titrate carefully. Regularly evaluate for adverse events such as respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Because oxycodone is known to be substantially excreted by the kidney, its clearance may decrease in patients with renal impairment. Initiate therapy with a lower than usual dosage of ROXYBOND and titrate carefully. Regularly evaluate for adverse events such as respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ROXYBOND contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

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

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

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

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

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

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

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

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

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

Risks Specific to Abuse of ROXYBOND

Abuse of ROXYBOND poses a risk of overdose and death. This risk is increased with concurrent use of ROXYBOND with alcohol and/or other CNS depressants.

ROXYBOND is for oral use only.

Parenteral abuse of ROXYBOND can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Injection of excipients included in the ROXYBOND formulation, intended to provide abuse-deterrent properties, may be associated with additional unknown serious risks. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Abuse Deterrence Studies

ROXYBOND is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse even if the tablet is subjected to physical manipulation and/or chemical extraction. To evaluate the ability of the abuse-deterrent technology to reduce the potential for abuse of ROXYBOND, a series of in vitro laboratory manipulation, extraction, and syringe ability studies were conducted. An in vivo intranasal clinical abuse potential study was also conducted.

In Vitro Testing

ROXYBOND has been tested in vitro using methods of manipulation that drug abusers commonly use for preparation of opioids for administration by various routes, including oral consumption, intranasal insufflation, and injection.

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Abusers may manipulate prescription opioids in order to prepare the tablets for oral, intranasal, or intravenous administration. The laboratory test data demonstrated that, relative to oxycodone immediate-release tablets, ROXYBOND has increased resistance to cutting, crushing, grinding, or breaking using selected tools. In addition, the intact and manipulated tablets resisted extraction in selected household and laboratory solvents under various conditions, including selected pre-treatments. Relative to oxycodone immediate-release tablets, the formulation forms a viscous material that resists passage through a needle; it was also more difficult to prepare solutions suitable for intravenous injection.

Clinical Abuse Potential Studies

A randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study in 29 non-dependent recreational opioid users with a history of intranasal drug abuse was performed to determine the relative bioavailability and abuse potential of crushed intranasal ROXYBOND 30 mg tablets compared with crushed intranasal 30 mg oxycodone immediate-release tablets and intact orally administered ROXYBOND 30 mg tablets. Intact oral ROXYBOND tablets were included as a reference for evaluating abuse potential after manipulation and administration via an unintended route.

Drug liking was measured on a 100-mm bipolar visual analog scale (VAS) where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would be willing to take the study drug again was also measured on a bipolar 0 to 100 VAS where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

The pharmacokinetic profiles of oxycodone were also determined in this study (Table 2). When crushed and insufflated, ROXYBOND showed a lower peak oxycodone plasma concentration (C_{max} ~28% reduction) and a 35% longer time to peak plasma concentration (T_{max}) relative to crushed and insufflated oxycodone immediate-release tablets. Similar results were demonstrated when crushed and insufflated ROXYBOND was compared to intact oral ROXYBOND with a reduction in C_{max} and a longer time to T_{max}. Intact oral ROXYBOND resulted in a C_{max} of oxycodone similar to that of crushed and insufflated oxycodone immediate-release tablets, with a similar T_{max}.

Table 2 Summary of Plasma Oxycodone Pharmacokinetic Parameters From the Intranasal Abuse Potential Study (n=31)

Treatment or Comparison	C_{max} (ng/mL) LS Mean	AUC_{0-t} (ng*hr/mL) LS Mean	T_{max} (hr) Median
Crushed, Insufflated oxycodone immediate-release tablets 30 mg	55.56	330.77	1.7
Crushed, Insufflated ROXYBOND 30 mg	40.04	309.21	2.3
Intact, oral ROXYBOND	56.97	265.38	1.3

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AUC_{0-t} = Area under the plasma concentration vs time curve from 0 to last measurable concentration.

Compared to crushed intranasal oxycodone immediate-release tablets, intranasal administration of crushed ROXYBOND was associated with statistically significantly lower drug liking (E_{max}) and take drug again (E_{max}) scores, as summarized in Table 3. Similar reductions in drug liking and willingness to take the drug again were reported for crushed intranasal ROXYBOND relative to intact oral ROXYBOND. These data are consistent with the slowing of the intended immediate-release properties of ROXYBOND when manipulated then insufflated compared to taking ROXYBOND orally intact. No statistically significant differences in E_{max} of Drug Liking or Take Drug Again were observed between crushed intranasal oxycodone immediate-release tablets and intact oral ROXYBOND.

Table 3. Summary of Maximum Drug Liking (E_{max}), and Take Drug Again (E_{max}), Following Administration of ROXYBOND, Oxycodone Immediate-release Tablets, and Placebo in Recreational Opioid Users (N=29)

VAS		Crushed Intranasal ROXYBOND 30 mg	Crushed Intranasal Oxycodone immediate-release tablets 30 mg	Intact Oral ROXYBOND 30 mg	Placebo
Drug Liking (E_{max})	Mean (SD)	71.1 (12.01)	82.9 (11.55)	81.5 (11.49)	53.4 (6.34)
	Median (Range)	71 (50 to 100)	82 (50 to 100)	82.00 (56 to 100)	51.0 (50 to 77)
Take Drug Again (E_{max})	Mean (SD)	62.2 (24.51)	82.1 (16.44)	77.3 (18.11)	41.9 (20.09)
	Median (Range)	62.0 (3 to 99)	86.0 (37 to 100)	81.0 (13 to 100)	50.0 (0.0 to 78)

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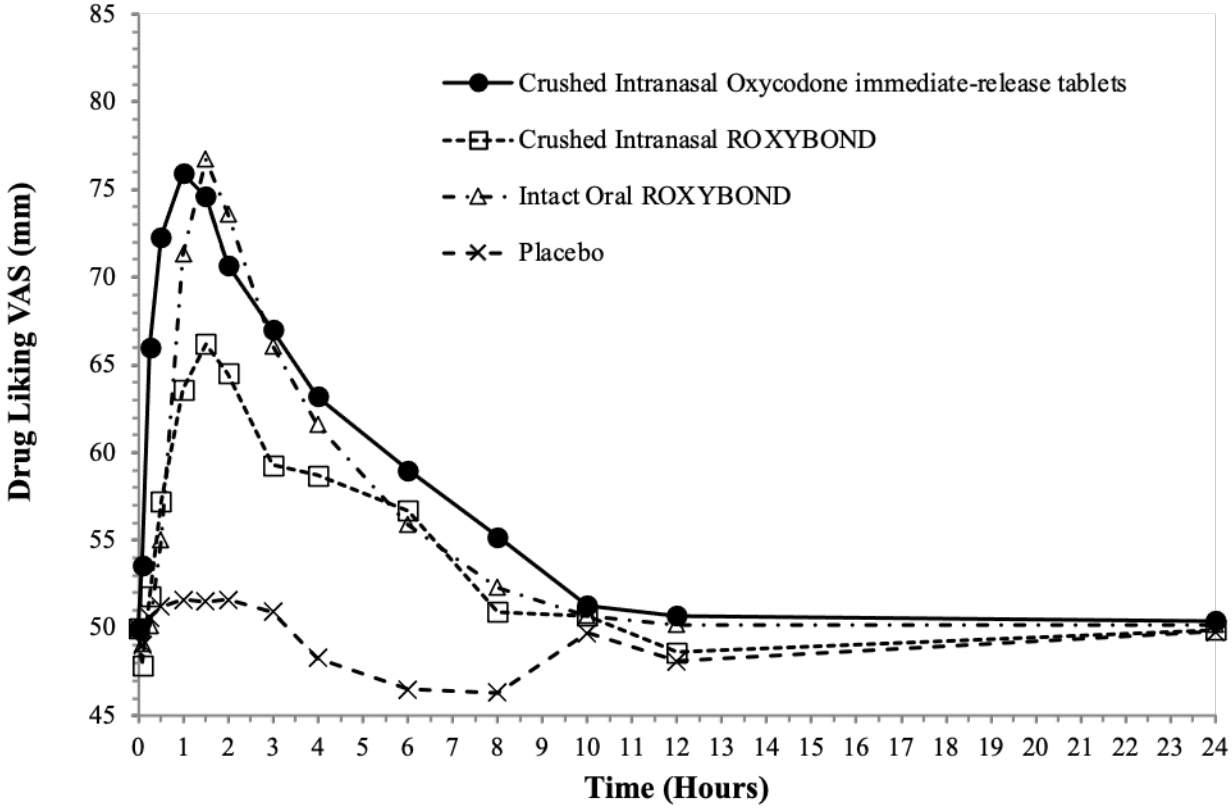
Figure 1. Mean Drug Liking VAS Scores Over Time (N=29)



The majority of subjects (86%; n=25) experienced some reduction in E_{max} of Drug Liking VAS with crushed intranasal ROXYBOND compared with crushed intranasal oxycodone immediate-release tablets, whereas 59% (n=17) experienced at least a 30% reduction in E_{max} of drug liking and 21% (n=6) experienced at least a 50% reduction in E_{max} of drug liking.

Summary

The in vitro data demonstrate that ROXYBOND has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that ROXYBOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by the intranasal, oral, and intravenous route is still possible.

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

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9.3 Dependence

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

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

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

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

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

When discontinuing ROXYBOND, gradually taper the dosage using a patient-specific plan that considers the following: the dose of ROXYBOND the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic *taper [see Dosage and Administration (2.5), and Warnings and Precautions (5.14)]*.

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

10 OVERDOSAGE

Clinical Presentation

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

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Treatment of Overdose

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

Opioid antagonists, such as naloxone, 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.

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in ROXYBOND, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

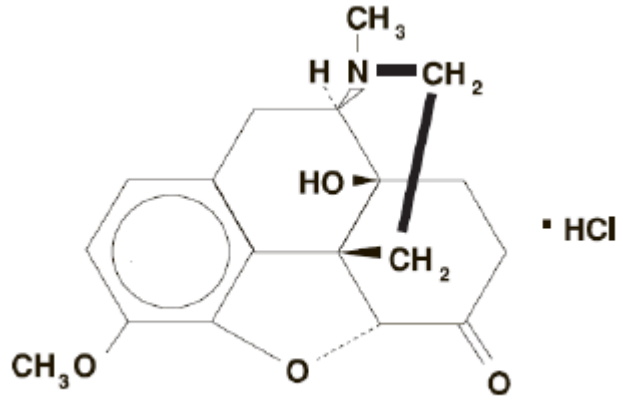
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered.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

11 DESCRIPTION

ROXYBOND (oxycodone hydrochloride) tablets for oral administration are available in 5 mg, 15 mg, and 30 mg strengths, each containing an equivalent of 4.5 mg, 13.5 mg, and 27 mg of oxycodone free base, respectively.

Oxycodone hydrochloride is an opioid agonist. It is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.82

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Each ROXYBOND tablet contains the following inactive ingredients common to all strengths: alginic acid, ammonium hydroxide, colloidal silicon dioxide, dibutyl sebacate, dimethylaminoethyl methacrylate copolymer, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, hypromellose, iron oxide black, isopropyl alcohol, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, n-butyl alcohol, polyethylene glycol, polysorbate 80, polyvinyl alcohol, propylene glycol, shellac in ethanol, sodium alginate, talc, titanium dioxide, and xanthan gum.

The 15 mg ROXYBOND tablets also contain: FD&C Blue No. 2 and iron oxide yellow.
The 30 mg ROXYBOND tablets also contain: FD&C Blue No. 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Effects on the Central Nervous System

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

Effects on Gastrointestinal Tract and Other Smooth Muscle

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

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Effects on Cardiovascular System

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

Effects on the Endocrine System

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

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

Effects on the Immune System

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

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

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)]*.

12.3 Pharmacokinetics

The activity of ROXYBOND tablets is primarily due to the parent drug oxycodone. ROXYBOND tablets are designed to provide immediate-release of oxycodone.

Oxycodone pharmacokinetics are similar for ROXYBOND and oxycodone immediate-release tablets. In the fasted state, the extent of absorption (AUC) is equivalent, the rate of absorption (C_{max}) is similar, and median T_{max} is slightly longer (1.0 to 1.8 h).

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Table 4. Pharmacokinetic Parameters (Mean ± SD)					
Dose\Parameters	**AUC_{0-t} (ng·hr/mL)**	**AUC_{0-inf} (ng·hr/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**Half Life (hr)**
Single Dose Pharmacokinetics Study					
ROXYBOND 5 mg tab (fasted)	45.5±15.4	49.0±16.1	8.3±2.1	1.5[a] (0.7 to 5.0)	3.9±1.2
ROXYBOND 15 mg tab (fasted)	127.5±38.1	131.6±39.0	22.0±5.8	1.7[a] (1.0 to 12.0)	4.1±0.8
ROXYBOND 30 mg tab (fasted)	277.0±89.6	285.8±94.1	48.5±15.9	1.5[a] (1.0 to 8.0)	4.3±1.0
Single Dose Food-Effect Study					
ROXYBOND 30 mg tab (fasted)	287.4±65.8	292.7±67.4	57.8±18.0	1.8[a] (0.8 to 5.0)	3.8±0.7
ROXYBOND 30 mg tab (fed)	354.2±82.5	361.9±86.7	68.0±20.1	2.0[a] (1.0 to 6.1)	3.9±0.6

[a] Median (range)

Absorption

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 presystemic and/or first-pass metabolism of oxycodone. Dose proportionality of oxycodone has been established using the ROXYBOND 5 mg, 15 mg, and 30 mg tablets based on maximum plasma concentration (C_{max}) and extent of absorption (AUC) (Figure 2). It takes approximately 18 to 24 hours to reach steady-state plasma concentrations of oxycodone with oxycodone hydrochloride.

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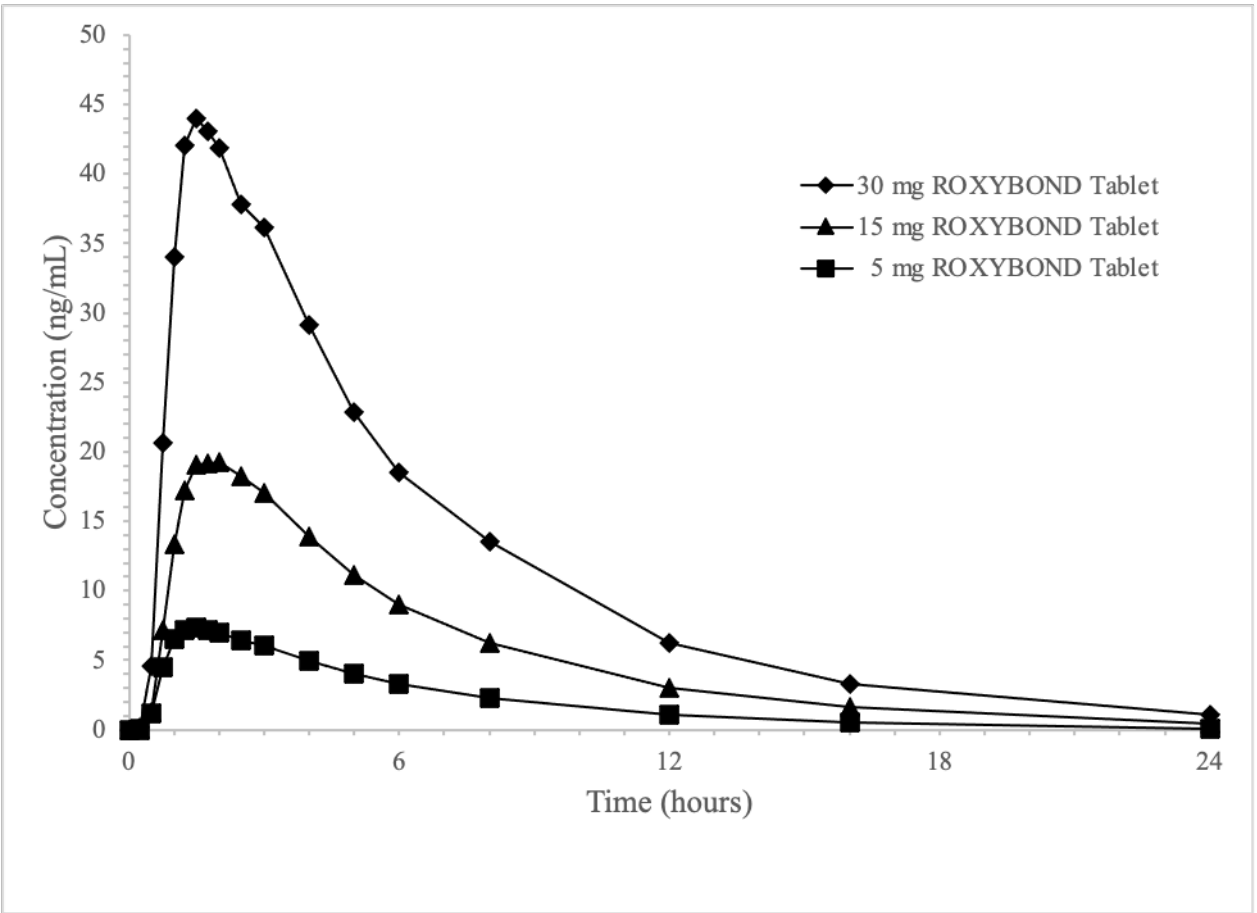
Figure 2. Mean Oxycodone Pharmacokinetic Profiles of 5-, 15-, 30-mg ROXYBOND Tablets (n=51)



Food Effect

A single-dose food effect study was conducted in normal volunteers using the 30-mg tablet. The concurrent intake of a high fat meal was shown to enhance the extent (23% increase in AUC), and the rate (18% increase in C_{max}) of oxycodone absorption from the 30-mg tablet (Table 4). In addition, food caused a slight delay in T_{max} (1.8 to 2 hours). Similar effects of food are expected with the 5-mg and 15-mg tablets.

Distribution

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

Elimination

Metabolism

A high proportion of oxycodone is N-dealkylated to noroxycodone during first-pass metabolism, and is catalyzed by CYP3A4. Oxymorphone is formed by the O-demethylation of oxycodone. The metabolism of oxycodone to oxymorphone is catalyzed by CYP2D6 *[see Drug Interactions (7)]*. Free and conjugated noroxycodone, free and conjugated oxycodone, and oxymorphone are excreted in human urine following a single oral dose of oxycodone. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the

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plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

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 not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of ROXYBOND was 3.8 to 4.3 hours.

Specific Populations

Age: Geriatric Patients

Population pharmacokinetic studies conducted with oxycodone hydrochloride, indicated that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65 *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment

In a clinical trial supporting the development of oxycodone hydrochloride tablets, too few patients with decreased hepatic function were evaluated to study these potential differences. However, because oxycodone is extensively metabolized in the liver, its clearance may decrease in hepatic impaired patients *[see Use in Specific Populations (8.6)]*.

Renal Impairment

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 *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Oxycodone hydrochloride 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).

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Impairment of Fertility

Studies in animals to evaluate the potential impact of oxycodone on fertility have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

ROXYBOND (oxycodone hydrochloride) tablets are supplied as 5 mg, 15 mg, and 30 mg strength round and color coated tablets with ink-prints on one side. The tablets are packaged in 100 tablet opaque HDPE bottles.

NDC	Strength	Tablet Shape	Tablet Color	Ink-Print on Tablet Side 1	Ink-Print on Tablet Side 2
81140-101-10	5 mg	Round coated tablets	White	IDT/O 5	None
81140-102-10	15 mg		Green	IDT/O 15	None
81140-103-10	30 mg		Blue	IDT/O 30	None

Dispense in a tight, light-resistant container, with a child-resistant closure. Protect from moisture.
Store at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions to 15°C to 30°C (59°F to 86°F).
Store ROXYBOND securely and dispose of properly.

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal:

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

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

Addiction, Abuse, and Misuse

Inform patients that the use of ROXYBOND, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions*

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(5.1)]. Instruct patients not to share ROXYBOND with others and to take steps to protect ROXYBOND from theft and misuse.

Life-Threatening Respiratory Depression

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2), Overdosage (10)]*.

Accidental Ingestion

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

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ROXYBOND is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with ROXYBOND. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

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

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

If naloxone is prescribed, also advise patients and caregivers:

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

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Hyperalgesia and Allodynia

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

Serotonin Syndrome

Inform patients that opioids 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 healthcare providers if they are taking, or plan to take serotonergic medication *[see Drug Interactions (7)]*.

MAOI Interaction

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

Important Administration Instructions

Instruct patients how to properly take ROXYBOND. Patients should be advised not to adjust the dose of ROXYBOND without consulting the prescribing healthcare provider *[see Dosage and Administration (2), Warnings and Precautions (5.14)]*.

Inform patients taking ROXYBOND that the medicine is absorbed by the body and the part of the tablet that contains inactive ingredients is eliminated from the body; patients may notice something that looks like a tablet in their stool.

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue ROXYBOND without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)]*.

Driving or Operating Machinery

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

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Healthcare professionals can telephone Protega Pharmaceuticals Inc. (1-844-798-3610) for information on this product.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting,

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anorexia, fatigue, weakness, dizziness and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.9)]*.

Hypotension

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

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in ROXYBOND. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6.2)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

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

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that ROXYBOND 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 breastfeeding women using ROXYBOND to carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct breastfeeding women to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

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Medication Guide
ROXYBOND (\'räk-sē- 'bänd\)
(oxycodone hydrochloride) tablets USP, CII

ROXYBOND is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid pain medicine, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An 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.

Important information about ROXYBOND:

- **Get emergency help or call 911 right away if you take too much ROXYBOND (overdose).** When you first start taking ROXYBOND, 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking ROXYBOND with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your ROXYBOND. They could die from taking it. Selling or giving away ROXYBOND is against the law.
- Store ROXYBOND securely, out of sight and reach of children and in a location not accessible by others, including visitors to the home.

Do not take ROXYBOND if you have:

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

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

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

Tell your healthcare provider if you are:

- **noticing your pain getting worse.** If your pain gets worse after you take ROXYBOND, do not take more of ROXYBOND without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking ROXYBOND.
- **pregnant or planning to become pregnant.** Use of ROXYBOND for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** ROXYBOND passes into breast milk and may harm your baby. Carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Seek immediate medical care if you notice these signs.
- Living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ROXYBOND with certain other medicines can cause serious side effects that could lead to death.

When taking ROXYBOND:

- Do not change your dose. Take ROXYBOND exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- For acute (short-term) pain, you may only need to take ROXYBOND for a few days. You may have some ROXYBOND left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused ROXYBOND.
- Take your prescribed dose every 4 to 6 hours as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking ROXYBOND regularly, do not stop taking ROXYBOND without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused ROXYBOND by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking ROXYBOND DO NOT:

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

The possible side effects of ROXYBOND are:

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

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

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

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

Manufactured for: Protega Pharmaceuticals Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: December 2023

GK-426