OXYCODONE HYDROCHLORIDE
EXTENDED-RELEASE TABLETS
10 mg, 20 mg, 40 mg, 80 mg*
*80 mg are for use in opioid-tolerant patients only
303374-0A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OXYCODONE HCl EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for OXYCODONE HCl EXTENDED-RELEASE TABLETS.

OXYCODONE HCl EXTENDED-RELEASE TABLETS, for oral use, CII
Initial U.S. Approval: 1950

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

- **OXYCODONE HCl EXTENDED-RELEASE TABLETS expose users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCODONE HCl EXTENDED-RELEASE TABLETS whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2)**
- **Accidental ingestion of OXYCODONE HCl EXTENDED-RELEASE TABLETS, especially in children, can result in a fatal overdose of oxycodone. (5.2)**
- **Prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone from OXYCODONE HCl EXTENDED-RELEASE TABLETS. (5.14)**

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

Boxed Warning	04/2014
Indications and Usage (1)	04/2014
Dosage and Administration (2)	04/2014
Warnings and Precautions (5)	04/2014

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

OXYCODONE HCl EXTENDED-RELEASE TABLETS are an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve OXYCODONE HCl EXTENDED-RELEASE TABLETS for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCODONE HCl EXTENDED-RELEASE TABLETS are not indicated as an as-needed (prn) analgesic. (1)

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

- OXYCODONE HCl EXTENDED-RELEASE TABLETS 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. (2.1)
- Do not abruptly discontinue OXYCODONE HCl EXTENDED-RELEASE TABLETS in a physically dependent patient. (2.4)
- Tablets must be swallowed intact and are not to be cut, broken, chewed, crushed, or dissolved (risk of potentially fatal dose). (2.5, 5.1)
- OXYCODONE HCl EXTENDED-RELEASE TABLETS should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. (2.5, 5.9, 17)

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

Extended-release tablets: 10 mg, 20 mg, 40 mg, and 80 mg (3)

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

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus and GI obstruction (4)
- Hypersensitivity to oxycodone (4)

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

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression and death. If coadminstration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Hypotensive effects: Monitor during dose initiation and titration. (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of OXYCODONE HCl EXTENDED-RELEASE TABLETS in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)
- Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. (5.9)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.14)

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

Most common adverse reactions (>5%) are constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with OXYCODONE HCl EXTENDED-RELEASE TABLETS because they may reduce analgesic effect of OXYCODONE HCl EXTENDED-RELEASE TABLETS or precipitate withdrawal symptoms. (7.4)

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

- Nursing mothers: Oxycodone has been detected in human milk. Closely monitor infants of nursing women receiving OXYCODONE HCl EXTENDED-RELEASE TABLETS. (8.3)
- Geriatrics: The initial dose may need to be reduced to 1/3 to 1/2 of the usual doses. (8.5)
- Hepatic impairment: Initiate therapy at 1/3 to 1/2 the usual doses and titrate carefully. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse
OXYCODONE HCl EXTENDED-RELEASE TABLETS expose 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 OXYCODONE HCl EXTENDED-RELEASE TABLETS and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCODONE HCl EXTENDED-RELEASE TABLETS. Monitor for respiratory depression, especially during initiation of OXYCODONE HCl EXTENDED-RELEASE TABLETS or following a dose increase. Instruct patients to swallow OXYCODONE HCl EXTENDED-RELEASE TABLETS whole; crushing, chewing, or dissolving OXYCODONE HCl EXTENDED-RELEASE TABLETS can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion
Accidental ingestion of even one dose of OXYCODONE HCl EXTENDED-RELEASE TABLETS, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction
The concomitant use of OXYCODONE HCl EXTENDED-RELEASE TABLETS with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCODONE HCl EXTENDED-RELEASE TABLETS and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.14) and Clinical Pharmacology (12.3)]*.

1 INDICATIONS AND USAGE

OXYCODONE HCl EXTENDED-RELEASE TABLETS are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCODONE HCl EXTENDED-RELEASE TABLETS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- OXYCODONE HCl EXTENDED-RELEASE TABLETS are not indicated as an as-needed (prn) analgesic

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

OXYCODONE HCl EXTENDED-RELEASE TABLETS should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCODONE HCl EXTENDED-RELEASE TABLETS 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with OXYCODONE HCl EXTENDED-RELEASE TABLETS *[see Warnings and Precautions (5.2)]*.

OXYCODONE HCl EXTENDED-RELEASE TABLETS must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving OXYCODONE HCl EXTENDED-RELEASE TABLETS will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

Use of OXYCODONE HCl EXTENDED-RELEASE TABLETS as the First Opioid Analgesic

Initiate treatment with OXYCODONE HCl EXTENDED-RELEASE TABLETS with one 10 mg tablet orally every 12 hours.

Use of OXYCODONE HCl EXTENDED-RELEASE TABLETS in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is OXYCODONE HCl EXTENDED-RELEASE TABLETS 10 mg orally every 12 hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from other Oral Oxycodone Formulations to OXYCODONE HCl EXTENDED-RELEASE TABLETS

Patients receiving other oral oxycodone formulations may be converted to OXYCODONE HCl EXTENDED-RELEASE TABLETS by administering one-half of the patient's total daily oral oxycodone dose as OXYCODONE HCl EXTENDED-RELEASE TABLETS every 12 hours.

Conversion from other Opioids to OXYCODONE HCl EXTENDED-RELEASE TABLETS

Discontinue all other around-the-clock opioid drugs when OXYCODONE HCl EXTENDED-RELEASE TABLETS therapy is initiated.

There are no established conversion ratios for conversion from other opioids to OXYCODONE HCl EXTENDED-RELEASE TABLETS defined by clinical trials. Discontinue all other around-the-clock opioid drugs when OXYCODONE HCl EXTENDED-RELEASE TABLETS therapy is initiated and initiate dosing using OXYCODONE HCl EXTENDED-RELEASE TABLETS 10 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone requirements which could result in adverse reactions. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products.

Conversion from Methadone to OXYCODONE HCl EXTENDED-RELEASE TABLETS

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to OXYCODONE HCl EXTENDED-RELEASE TABLETS

Eighteen hours following the removal of the transdermal fentanyl patch, OXYCODONE HCl EXTENDED-RELEASE TABLETS treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg every 12 hours of OXYCODONE HCl EXTENDED-RELEASE TABLETS, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCODONE HCl EXTENDED-RELEASE TABLETS, as there is limited documented experience with this conversion.

2.2 Titration and Maintenance of Therapy

Individually titrate OXYCODONE HCl EXTENDED-RELEASE TABLETS to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OXYCODONE HCl EXTENDED-RELEASE TABLETS to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse and misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of OXYCODONE HCl EXTENDED-RELEASE TABLETS or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the OXYCODONE HCl EXTENDED-RELEASE TABLETS dose. Because steady-state plasma concentrations are approximated in 1 day, OXYCODONE HCl EXTENDED-RELEASE TABLETS dosage may be adjusted every 1 to 2 days. If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

2.3 Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

2.4 Discontinuation of OXYCODONE HCl EXTENDED-RELEASE TABLETS

When the patient no longer requires therapy with OXYCODONE HCl EXTENDED-RELEASE TABLETS, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue OXYCODONE HCl EXTENDED-RELEASE TABLETS.

2.5 Administration of OXYCODONE HCl EXTENDED-RELEASE TABLETS

Instruct patients to swallow OXYCODONE HCl EXTENDED-RELEASE TABLETS intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.1)]*.

Instruct patients to take OXYCODONE HCl EXTENDED-RELEASE TABLETS one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth *[see Warnings and Precautions (5.9) and Patient Counseling Information (17)]*.

3 DOSAGE FORMS AND STRENGTHS

- 10 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
- 20 mg film-coated extended-release tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
- 40 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
- 80 mg film-coated extended-release tablets* (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

*** 80 mg tablets for use in opioid-tolerant patients only**

4 CONTRAINDICATIONS

OXYCODONE HCl EXTENDED-RELEASE TABLETS are contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus and gastrointestinal obstruction
- Hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

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

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCODONE HCl EXTENDED-RELEASE TABLETS. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse or misuse prior to prescribing OXYCODONE HCl EXTENDED-RELEASE TABLETS, and monitor all patients receiving OXYCODONE HCl EXTENDED-RELEASE TABLETS for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol 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 modified-release opioid formulations such as OXYCODONE HCl EXTENDED-RELEASE TABLETS, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCODONE HCl EXTENDED-RELEASE TABLETS along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse, or misuse of OXYCODONE HCl EXTENDED-RELEASE TABLETS by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death *[see Overdosage (10)]*.

Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCODONE HCl EXTENDED-RELEASE TABLETS. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact 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 modified-release opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OXYCODONE HCl EXTENDED-RELEASE TABLETS, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with OXYCODONE HCl EXTENDED-RELEASE TABLETS and following dose increases.

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

Accidental ingestion of even one dose of OXYCODONE HCl EXTENDED-RELEASE TABLETS, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can result in withdrawal signs 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. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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.

5.4 Interactions with Central Nervous System Depressants

Hypotension and profound sedation, coma, or respiratory depression may result if OXYCODONE HCl EXTENDED-RELEASE TABLETS are used concomitantly with other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of OXYCODONE HCl EXTENDED-RELEASE TABLETS in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that can cause CNS depression. If the decision to begin OXYCODONE HCl EXTENDED-RELEASE TABLETS therapy is made, start with 1/3 to 1/2 the usual dose of OXYCODONE HCl EXTENDED-RELEASE TABLETS, monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.1) and Dosage and Administration (2.2)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating OXYCODONE HCl EXTENDED-RELEASE TABLETS and when OXYCODONE HCl EXTENDED-RELEASE TABLETS are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with OXYCODONE HCl EXTENDED-RELEASE TABLETS, as in these patients, even usual therapeutic doses of OXYCODONE HCl EXTENDED-RELEASE TABLETS may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Hypotensive Effects

OXYCODONE HCl EXTENDED-RELEASE TABLETS may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7.1)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of OXYCODONE HCl EXTENDED-RELEASE TABLETS. In patients with circulatory shock, OXYCODONE HCl EXTENDED-RELEASE TABLETS may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OXYCODONE HCl EXTENDED-RELEASE TABLETS in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking OXYCODONE HCl EXTENDED-RELEASE TABLETS who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with OXYCODONE HCl EXTENDED-RELEASE TABLETS. OXYCODONE HCl EXTENDED-RELEASE TABLETS may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of OXYCODONE HCl EXTENDED-RELEASE TABLETS in patients with impaired consciousness or coma.

5.9 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing OXYCODONE HCl EXTENDED-RELEASE TABLETS. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OXYCODONE HCl EXTENDED-RELEASE TABLETS prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.10 Use in Patients with Gastrointestinal Conditions

OXYCODONE HCl EXTENDED-RELEASE TABLETS are contraindicated in patients with GI obstruction, including paralytic ileus. The oxycodone in OXYCODONE HCl EXTENDED-RELEASE TABLETS may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may cause increases in the serum amylase.

5.11 Use in Patients with Convulsive or Seizure Disorders

The oxycodone in OXYCODONE HCl EXTENDED-RELEASE TABLETS may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during OXYCODONE HCl EXTENDED-RELEASE TABLETS therapy.

5.12 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including OXYCODONE HCl EXTENDED-RELEASE TABLETS. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing OXYCODONE HCl EXTENDED-RELEASE TABLETS, gradually taper the dose *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue OXYCODONE HCl EXTENDED-RELEASE TABLETS.

5.13 Driving and Operating Machinery

OXYCODONE HCl EXTENDED-RELEASE TABLETS 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 OXYCODONE HCl EXTENDED-RELEASE TABLETS and know how they will react to the medication.

5.14 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of OXYCODONE HCl EXTENDED-RELEASE TABLETS, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.

Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid effects.

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.

If co-administration is necessary, caution is advised when initiating OXYCODONE HCl EXTENDED-RELEASE TABLETS treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

5.15 Laboratory Monitoring

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

6 ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Hypotensive Effects *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trial 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.

The safety of OXYCODONE HCl EXTENDED-RELEASE TABLETS was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OXYCODONE HCl EXTENDED-RELEASE TABLETS in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OXYCODONE HCl EXTENDED-RELEASE TABLETS may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OXYCODONE HCl EXTENDED-RELEASE TABLETS with placebo are shown in Table 1 below:

TABLE 1: Common Adverse Reactions (>5%)

Adverse Reaction	OXYCODONE HCl EXTENDED-RELEASE TABLETS (n=227)	Placebo (n=45)
	(%)	(%)
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OXYCODONE HCl EXTENDED-RELEASE TABLETS with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis
General disorders and administration site conditions: chills, fever
Metabolism and nutrition disorders: anorexia
Musculoskeletal and connective tissue disorders: twitching
Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities
Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups
Skin and subcutaneous tissue disorders: rash
Vascular disorders: postural hypotension

The following adverse reactions occurred **in less than 1% of patients** involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy
Ear and labyrinth disorders: tinnitus
Eye disorders: abnormal vision
Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis
General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema
Injury, poisoning and procedural complications: accidental injury
Investigations: ST depression
Metabolism and nutrition disorders: dehydration
Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion
Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination
Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention
Reproductive system and breast disorders: impotence
Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration
Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of controlled-release oxycodone: abuse, addiction, amenorrhea, cholestasis, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

Anaphylaxis has been reported with ingredients contained in OXYCODONE HCl EXTENDED-RELEASE TABLETS. Advise patients how to recognize such a reaction and when to seek medical attention.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

7 DRUG INTERACTIONS

7.1 CNS Depressants

The concomitant use of OXYCODONE HCl EXTENDED-RELEASE TABLETS and other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma, or death. Monitor patients receiving CNS depressants and OXYCODONE HCl EXTENDED-RELEASE TABLETS for signs of respiratory depression, sedation, and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.

7.2 Muscle Relaxants

Oxycodone may enhance the neuromuscular blocking action of true skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and OXYCODONE HCl EXTENDED-RELEASE TABLETS for signs of respiratory depression that may be greater than otherwise expected.

7.3 Drugs Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4 and 2D6

Because the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations and result in increased or prolonged opioid effects. These effects could me more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration with OXYCODONE HCl EXTENDED-RELEASE TABLETS is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4

CYP450 3A4 inducers may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration with OXYCODONE HCl EXTENDED-RELEASE TABLETS is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression *[see Clinical Pharmacology (12.3)]*.

7.4 Mixed Agonist/Antagonist and Partial Agonists Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of oxycodone or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving OXYCODONE HCl EXTENDED-RELEASE TABLETS.

7.5 Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.

7.6 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when OXYCODONE HCl EXTENDED-RELEASE TABLETS are used concurrently with anticholinergic drugs.

This document contains two full Medication Guides: Please fold and tear along perforation to separate.

Medication Guide
Oxycodone (OX-ee-KOH-dohn) HCl Extended-Release Tablets, CII

OXYCODONE HCl EXTENDED-RELEASE TABLETS are:

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

Important information about OXYCODONE HCl EXTENDED-RELEASE TABLETS:

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

Do not take OXYCODONE HCl EXTENDED-RELEASE TABLETS if you have:

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

Before taking OXYCODONE HCl EXTENDED-RELEASE TABLETS, 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, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** OXYCODONE HCl EXTENDED-RELEASE TABLETS pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCODONE HCl EXTENDED-RELEASE TABLETS with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCODONE HCl EXTENDED-RELEASE TABLETS:

- Do not change your dose. Take OXYCODONE HCl EXTENDED-RELEASE TABLETS exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.

Continued on the back

This document contains two full Medication Guides: Please fold and tear along perforation to separate.

Medication Guide
Oxycodone (OX-ee-KOH-dohn) HCl Extended-Release Tablets, CII

OXYCODONE HCl EXTENDED-RELEASE TABLETS are:

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

Important information about OXYCODONE HCl EXTENDED-RELEASE TABLETS:

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

Do not take OXYCODONE HCl EXTENDED-RELEASE TABLETS if you have:

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

Before taking OXYCODONE HCl EXTENDED-RELEASE TABLETS, 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, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** OXYCODONE HCl EXTENDED-RELEASE TABLETS pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCODONE HCl EXTENDED-RELEASE TABLETS with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCODONE HCl EXTENDED-RELEASE TABLETS:

- Do not change your dose. Take OXYCODONE HCl EXTENDED-RELEASE TABLETS exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.

Continued on the back

Continued from the front

- Swallow OXYCODONE HCl EXTENDED-RELEASE TABLETS whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCODONE HCl EXTENDED-RELEASE TABLETS because this may cause you to overdose and die.
- OXYCODONE HCl EXTENDED-RELEASE TABLETS should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCODONE HCl EXTENDED-RELEASE TABLETS without talking to your healthcare provider.**
- After you stop taking OXYCODONE HCl EXTENDED-RELEASE TABLETS, flush any unused tablets down the toilet.

While taking OXYCODONE HCl EXTENDED-RELEASE TABLETS DO NOT:

- Drive or operate heavy machinery, until you know how OXYCODONE HCl EXTENDED-RELEASE TABLETS affect you. OXYCODONE HCl EXTENDED-RELEASE TABLETS 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 OXYCODONE HCl EXTENDED-RELEASE TABLETS may cause you to overdose and die.

The possible side effects of OXYCODONE HCl EXTENDED-RELEASE TABLETS are:

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

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

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

Distributed by: Par Pharmaceutical Companies, Inc., Spring Valley, NY 10977, **www.parpharm.com or call 1-800-828-9393**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: April 2014

OS136-01-55-01
MG136-01-55-01

Continued from the front

- Swallow OXYCODONE HCl EXTENDED-RELEASE TABLETS whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCODONE HCl EXTENDED-RELEASE TABLETS because this may cause you to overdose and die.
- OXYCODONE HCl EXTENDED-RELEASE TABLETS should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCODONE HCl EXTENDED-RELEASE TABLETS without talking to your healthcare provider.**
- After you stop taking OXYCODONE HCl EXTENDED-RELEASE TABLETS, flush any unused tablets down the toilet.

While taking OXYCODONE HCl EXTENDED-RELEASE TABLETS DO NOT:

- Drive or operate heavy machinery, until you know how OXYCODONE HCl EXTENDED-RELEASE TABLETS affect you. OXYCODONE HCl EXTENDED-RELEASE TABLETS 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 OXYCODONE HCl EXTENDED-RELEASE TABLETS may cause you to overdose and die.

The possible side effects of OXYCODONE HCl EXTENDED-RELEASE TABLETS are:

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

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

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

Distributed by: Par Pharmaceutical Companies, Inc., Spring Valley, NY 10977, **www.parpharm.com or call 1-800-828-9393**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: April 2014

OS136-01-55-01
MG136-01-55-01

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Teratogenic Effects - Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. OXYCODONE HCl EXTENDED-RELEASE TABLETS should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

The effect of oxycodone in human reproduction has not been adequately studied. Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no long-term developmental or reproductive effects in the pups *[see Nonclinical Toxicology (13.1)]*.

Non-Teratogenic Effects

Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. OXYCODONE HCl EXTENDED-RELEASE TABLETS are not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics 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 dilatation, which tends to shorten labor.

8.3 Nursing Mothers

Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OXYCODONE HCl EXTENDED-RELEASE TABLETS. Do not initiate OXYCODONE HCl EXTENDED-RELEASE TABLETS therapy while nursing because of the possibility of sedation or respiratory depression in the infant.

Withdrawal signs can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

Safety and effectiveness of OXYCODONE HCl EXTENDED-RELEASE TABLETS in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, reduce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OXYCODONE HCl EXTENDED-RELEASE TABLETS cautiously in these patients.

8.6 Hepatic Impairment

A study of OXYCODONE HCl EXTENDED-RELEASE TABLETS in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation *[see Clinical Pharmacology (12.3)]*.

8.8 Gender Differences

In pharmacokinetic studies with OXYCODONE HCl EXTENDED-RELEASE TABLETS, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OXYCODONE HCl EXTENDED-RELEASE TABLETS contain oxycodone, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCODONE HCl EXTENDED-RELEASE TABLETS can be abused and are subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

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

9.2 Abuse

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

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get "high", or the use of steroids for performance enhancement and muscle build up.

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

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OXYCODONE HCl EXTENDED-RELEASE TABLETS, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state 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 reduce abuse of opioid drugs.

Risks Specific to Abuse of OXYCODONE HCl EXTENDED-RELEASE TABLETS

OXYCODONE HCl EXTENDED-RELEASE TABLETS are for oral use only. Abuse of OXYCODONE HCl EXTENDED-RELEASE TABLETS pose a risk of overdose and death. The risk is increased with concurrent use of OXYCODONE HCl EXTENDED-RELEASE TABLETS with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCODONE HCl EXTENDED-RELEASE TABLETS enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCODONE HCl EXTENDED-RELEASE TABLETS can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

OXYCODONE HCl EXTENDED-RELEASE TABLETS are formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCODONE HCl EXTENDED-RELEASE TABLETS resulting from a change in formulation, in this section, the original formulation of OXYCODONE HCl EXTENDED-RELEASE TABLETS, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as "OXYCODONE HCl EXTENDED-RELEASE TABLETS".

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCODONE HCl EXTENDED-RELEASE TABLETS to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCODONE HCl EXTENDED-RELEASE TABLETS relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCODONE HCl EXTENDED-RELEASE TABLETS gradually form a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS 30 mg tablets, coarsely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 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 take the study drug again was also measured on a bipolar scale of 0 to 100 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").

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 2.

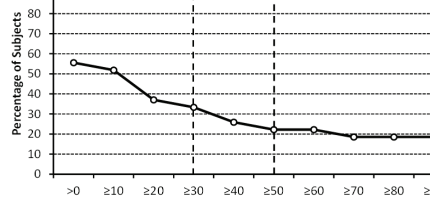
Table 2: Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

VAS Scale (100 mm)*		OXYCODONE HCl EXTENDED-RELEASE TABLETS (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36 – 100)	100 (51 – 100)	100 (50 – 100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0 – 100)	100 (20 – 100)	100 (0 – 100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCODONE HCl EXTENDED-RELEASE TABLETS vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCODONE HCl EXTENDED-RELEASE TABLETS relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCODONE HCl EXTENDED-RELEASE TABLETS relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCODONE HCl EXTENDED-RELEASE TABLETS compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCODONE HCl EXTENDED-RELEASE TABLETS compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OXYCODONE HCl EXTENDED-RELEASE TABLETS vs. oxycodone HCl, N=27 Following Intranasal Administration



Percent Reduction in Drug Liking for Finely Crushed Oxycodone HCl Extended-Release Tablets vs. Powdered Oxycodone HCl Following Intranasal Administration

The results of a similar analysis of drug liking for finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCODONE HCl EXTENDED-RELEASE TABLETS relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OXYCODONE HCl EXTENDED-RELEASE TABLETS relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCODONE HCl EXTENDED-RELEASE TABLETS compared to original OxyContin.

Summary

The *in vitro* data demonstrate that OXYCODONE HCl EXTENDED-RELEASE TABLETS have physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCODONE HCl EXTENDED-RELEASE TABLETS have physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCODONE HCl EXTENDED-RELEASE TABLETS by these routes, as well as by the oral route, is still possible.

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

OXYCODONE HCl EXTENDED-RELEASE TABLETS contain oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCODONE HCl EXTENDED-RELEASE TABLETS can be abused and are subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

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

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

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

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

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with OXYCODONE HCl EXTENDED-RELEASE TABLETS 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, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

Treatment of Overdose

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

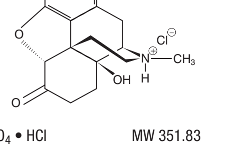
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on OXYCODONE HCl EXTENDED-RELEASE TABLETS. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Because the duration of reversal would be expected to be less than the duration of action of oxycodone in OXYCODONE HCl EXTENDED-RELEASE TABLETS, carefully monitor the patient until spontaneous respiration is reliably reestablished. OXYCODONE HCl EXTENDED-RELEASE TABLETS will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the usual dose 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 begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OXYCODONE HCl EXTENDED-RELEASE TABLETS are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \bullet HCl$ MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

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

The 10 mg, 20 mg, 40 mg, and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 20 mg tablets also contain polysorbate 80 and red iron oxide.

The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.

The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

12 CLINICAL PHARMACOLOGY

Oxycodone hydrochloride is a full opioid agonist and is relatively selective for the mu 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 to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

12.1 Mechanism of Action

Central Nervous System

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

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OXYCODONE HCl EXTENDED-RELEASE TABLETS (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. OXYCODONE HCl EXTENDED-RELEASE TABLETS doses of 20 mg and 30 mg produced statistically significant pain reduction compared to placebo.

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in CO_2 tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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 origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose *[see Overdosage (10)]*.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

Effects on the Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective "drug effect", analgesia and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. 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.

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 side effects.

The dose of OXYCODONE HCl EXTENDED-RELEASE TABLETS must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients *[see Dosage and Administration (2.1)]*.

12.3 Pharmacokinetics

The activity of OXYCODONE HCl EXTENDED-RELEASE TABLETS is primarily due to the parent drug oxycodone. OXYCODONE HCl EXTENDED-RELEASE TABLETS are designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OXYCODONE HCl EXTENDED-RELEASE TABLETS impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OXYCODONE HCl EXTENDED-RELEASE TABLETS is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OXYCODONE HCl EXTENDED-RELEASE TABLETS to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OXYCODONE HCl EXTENDED-RELEASE TABLETS in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life ($t_{½}$) of oxycodone following the administration of OXYCODONE HCl EXTENDED-RELEASE TABLETS was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Plasma Oxycodone Concentration over Time

Dose proportionality has been established for OXYCODONE HCl EXTENDED-RELEASE TABLETS 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) *(see Table 3)*. Given the short elimination $t_{½}$ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OXYCODONE HCl EXTENDED-RELEASE TABLETS. In a study comparing 10 mg of OXYCODONE HCl EXTENDED-RELEASE TABLETS every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

TABLE 3

Mean [% coefficient of variation]

Regimen	Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	T_{max} (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

* for single-dose AUC = AUC_{0-inf}

† data obtained while subjects received naltrexone, which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OXYCODONE HCl EXTENDED-RELEASE TABLETS.

Distribution

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.3)]*.

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7.3)]*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Geriatric Use

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Gender

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown *[see Use in Specific Populations (8.8)]*.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination $t_{½}$ for oxycodone of 1 hour.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination t½ for oxycodone increased by 2.3 hours.

Drug-Drug Interactions

CYP3A4 Inhibitors

CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of OXYCODONE HCl EXTENDED-RELEASE TABLETS (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7.3)]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7.3)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with OXYCODONE HCl EXTENDED-RELEASE TABLETS *[see Drug Interactions (7.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

Mutagenesis

Oxycodone was genotoxic in the mouse lymphoma assay at concentrations of 50 mcg/mL or greater with metabolic activation and at 400 mcg/mL or greater without metabolic activation. Clastogenicity was observed with oxycodone in the presence of metabolic activation in one chromosomal aberration assay in human lymphocytes at concentrations greater than or equal to 1250 mcg/mL at 24 but not 48 hours of exposure. In a second chromosomal aberration assay with human lymphocytes, no structural clastogenicity was observed either with or without metabolic activation; however, in the absence of metabolic activation, oxycodone increased numerical chromosomal aberrations (polyploidy). Oxycodone was not genotoxic in the following assays: Ames *S. typhimurium* and *E. coli* test with and without metabolic activation at concentrations up to 5000 μg/plate, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at concentrations up to 1500 μg/mL, and with activation after 48 hours of exposure at concentrations up to 5000 μg/mL, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels up to 48 μg/mL).

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to gestation day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (≤ 8 mg/kg/day).

14 CLINICAL STUDIES

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OXYCODONE HCl EXTENDED-RELEASE TABLETS 20 mg, but not 10 mg, were statistically significant in pain reduction compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

OXYCODONE HCl EXTENDED-RELEASE TABLETS 10 mg are film-coated, round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 **(NDC 49884-136-01)**.

OXYCODONE HCl EXTENDED-RELEASE 20 mg are film-coated, round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 **(NDC 49884-137-01)**.

OXYCODONE HCl EXTENDED-RELEASE TABLETS 40 mg are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 **(NDC 49884-138-01)**.

OXYCODONE HCl EXTENDED-RELEASE TABLETS 80 mg are film-coated, round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 **(NDC 49884-197-01)**.

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

CAUTION

DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION

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

Addiction, Abuse and Misuse

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

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression including information that the risk is greatest when starting OXYCODONE HCl EXTENDED-RELEASE TABLETS or when the dose is increased and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store OXYCODONE HCl EXTENDED-RELEASE TABLETS securely and to dispose of unused OXYCODONE HCl EXTENDED-RELEASE TABLETS by flushing the tablets down the toilet.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3)]*.

Interactions with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur if OXYCODONE HCl EXTENDED-RELEASE TABLETS are used with other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly take OXYCODONE HCl EXTENDED-RELEASE TABLETS, including the following:

- OXYCODONE HCl EXTENDED-RELEASE TABLETS are designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OXYCODONE HCl EXTENDED-RELEASE TABLETS can result in a fatal overdose.
- OXYCODONE HCl EXTENDED-RELEASE TABLETS should be taken one tablet at a time.
- Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.

Hypotension

Inform patients that OXYCODONE HCl EXTENDED-RELEASE TABLETS 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 a sitting or lying position).

Driving or Operating Heavy Machinery

Inform patients that OXYCODONE HCl EXTENDED-RELEASE TABLETS may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in OXYCODONE HCl EXTENDED-RELEASE TABLETS. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that OXYCODONE HCl EXTENDED-RELEASE TABLETS can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Disposal of Unused OXYCODONE HCl EXTENDED-RELEASE TABLETS

Advise patients to flush the unused tablets down the toilet when OXYCODONE HCl EXTENDED-RELEASE TABLETS are no longer needed.

Healthcare professionals can telephone Par Pharmaceutical Companies, Inc. at 1-800-828-9393 for information on this product.

Manufactured by:
Purdue Pharmaceuticals L.P.
Wilson, NC 27893

Distributed by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

U.S. Patent Numbers 6,488,963; 7,129,248; 7,674,799; 7,674,800; 7,683,072; 7,776,314; 8,114,383; 8,309,060; and 8,337,888.

Medication Guide

Oxycodone (OX-ee-KOH-dohn) HCl Extended-Release Tablets, CII

OXYCODONE HCl EXTENDED-RELEASE TABLETS are:

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

Important information about OXYCODONE HCl EXTENDED-RELEASE TABLETS:

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

Do not take OXYCODONE HCl EXTENDED-RELEASE TABLETS if you have:

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

Before taking OXYCODONE HCl EXTENDED-RELEASE TABLETS, 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, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OXYCODONE HCl EXTENDED-RELEASE TABLETS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** OXYCODONE HCl EXTENDED-RELEASE TABLETS pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCODONE HCl EXTENDED-RELEASE TABLETS with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCODONE HCl EXTENDED-RELEASE TABLETS:

- Do not change your dose. Take OXYCODONE HCl EXTENDED-RELEASE TABLETS exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OXYCODONE HCl EXTENDED-RELEASE TABLETS whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCODONE HCl EXTENDED-RELEASE TABLETS because this may cause you to overdose and die.
- OXYCODONE HCl EXTENDED-RELEASE TABLETS should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCODONE HCl EXTENDED-RELEASE TABLETS without talking to your healthcare provider.**
- After you stop taking OXYCODONE HCl EXTENDED-RELEASE TABLETS, flush any unused tablets down the toilet.

While taking OXYCODONE HCl EXTENDED-RELEASE TABLETS DO NOT:

- Drive or operate heavy machinery, until you know how OXYCODONE HCl EXTENDED-RELEASE TABLETS affect you. OXYCODONE HCl EXTENDED-RELEASE TABLETS 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 OXYCODONE HCl EXTENDED-RELEASE TABLETS may cause you to overdose and die.

The possible side effects of OXYCODONE HCl EXTENDED-RELEASE TABLETS are:

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

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

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

Distributed by: Par Pharmaceutical Companies, Inc., Spring Valley, NY 10977, **www.parpharm.com or call 1-800-828-9393**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: April 2014

OS136-01-55-01
303374-0A