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

OxyContin® (oxycodone hydrochloride controlled-release) Tablets, for oral use, CII
Initial U.S. Approval: 1950

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE
See full prescribing information for complete boxed warning.

- **OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy (5.1, 9).**
- **Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of OxyContin tablets to reduce the risk (5.2).**
- **Accidental ingestion of OxyContin can result in fatal overdose of oxycodone, especially in children (5.3).**

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

Boxed Warning	07/2012
Indications and Usage (1)	07/2012
Dosage and Administration (2)	09/2012
Contraindications (4)	07/2012
Warnings and Precautions (5)	07/2012

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

OxyContin is an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

- OxyContin is not for use:
  - As an as-needed (prn) analgesic (1)
  - For pain that is mild or not expected to persist for an extended period of time (1)
  - For acute pain (1)
  - In the immediate postoperative period (1)
  - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)
- OxyContin 60 mg and 80 mg tablets are only for patients in whom tolerance to an opioid of comparable potency is established. (1)

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

- Individualize dosing based on patient's prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2)
- Do not abruptly discontinue OxyContin 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)

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

- Tablets: 10 mg, 15 mg, 20 mg , 30 mg, 40 mg, 60 mg, and 80 mg (3)

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

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

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

- Elderly, cachectic, and debilitated patients, and patients with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.4, 5.5)
- Interaction with CNS depressants: Consider dose reduction of one or both drugs because of additive effects. (5.6, 7.1)
- 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 OxyContin in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.13)

----------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 Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- Muscle relaxants: Avoid use with OxyContin because of increased risk of respiratory depression. (7.2)
- The CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin. Drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. (7.3)
- Mixed agonist/antagonist opioid analgesics: Avoid use with OxyContin because they may reduce analgesic effect of OxyContin 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 OxyContin. (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: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Initial Dosing
2.2 Titration and Maintenance of Therapy
2.3 Patients with Hepatic Impairment
2.4 Discontinuation of OxyContin
2.5 Administration of OxyContin
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Abuse Potential
5.2 Life-Threatening Respiratory Depression
5.3 Accidental Exposure
5.4 Elderly, Cachectic, and Debilitated Patients
5.5 Use in Patients with Chronic Pulmonary Disease
5.6 Interactions with Alcohol, CNS Depressants, and Illicit Drugs
5.7 Hypotensive Effects
5.8 Use in Patients with Head Injury or Increased Intracranial Pressure
5.9 Use in Patients with Gastrointestinal Conditions
5.10 Use in Patients with Convulsive or Seizure Disorders
5.11 Avoidance of Withdrawal
5.12 Driving and Operating Machinery
5.13 Cytochrome P450 3A4 Inhibitors and Inducers
5.14 Laboratory Monitoring
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 CNS Depressants
7.2 Muscle Relaxants
7.3 Agents Affecting Cytochrome P450 Isoenzymes
7.4 Mixed Agonist/Antagonist Opioid Analgesics
7.5 Diuretics

7.6 Anticholinergics
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
8.8 Gender Differences
8.9 Neonatal Opioid Withdrawal Syndrome
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

OxyContin® contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit *[see Warnings and Precautions (5.1)]*. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is 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 depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment *[see Drug Abuse and Dependence (9)]*.

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused *[see Warnings and Precautions (5.2)]*. Proper dosing and titration are essential and OxyContin should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OxyContin or following a dose increase. Instruct patients to swallow OxyContin tablets intact. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Exposure

Accidental ingestion of OxyContin, especially in children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

OxyContin is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- In the immediate postoperative period (the first 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid tolerant are those who are taking 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 for one week or longer.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with OxyContin *[see Warnings and Precautions (5.2)]*.

Consider the following factors when selecting an initial dose of OxyContin:

- Total daily dose, potency, and any prior opioid the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of oxycodone needed (Note: potency estimates may vary with the route of administration);
- Patient's degree of opioid experience and opioid tolerance;
- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.

Use of OxyContin as the First Opioid Analgesic

Initiate therapy with 10 mg every 12 hours.

Conversion from other Oral Oxycodone Formulations to OxyContin

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

Conversion from other Opioids to OxyContin

While there are useful tables of oral and parenteral equivalents, there is substantial inter-patient variation in the relative potency of different opioid drugs and formulations. Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. As such, it is safer to underestimate a patient's 24-hour oral oxycodone requirement and provide rescue medication (e.g., immediate-release oxycodone) than to overestimate and precipitate an adverse reaction. In general, begin with half of the estimated daily oxycodone requirement as the initial daily OxyContin estimate, then divide into two doses

taken 12 hours apart, and manage inadequate analgesia by supplementation with immediate-release oxycodone.

Published relative potency data are available and may be referred to in clinical practice guidelines such as those published by authorities in the field of pain medicine, but such ratios are approximations. Consider contacting your specific state medical or pharmacy professional societies for further information on how to safely convert patients from one opioid to another.

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin 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 OxyContin, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OxyContin, as there is limited documented experience with this conversion.

2.2 Titration and Maintenance of Therapy

Individually titrate OxyContin to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OxyContin to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the OxyContin dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in 1 day, OxyContin dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the next 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 OxyContin

When the patient no longer requires therapy with OxyContin 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 OxyContin.

2.5 Administration of OxyContin

Instruct patients to swallow OxyContin 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, 5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

- 10 mg film-coated tablets (round, white-colored, bi-convex tablets debossed with OC on one side and 10 on the other)
- 15 mg film-coated tablets (round, gray-colored, bi-convex tablets debossed with OC on one side and 15 on the other)
- 20 mg film-coated tablets (round, pink-colored, bi-convex tablets debossed with OC on one side and 20 on the other)
- 30 mg film-coated tablets (round, brown-colored, bi-convex tablets debossed with OC on one side and 30 on the other)
- 40 mg film-coated tablets (round, yellow-colored, bi-convex tablets debossed with OC on one side and 40 on the other)
- 60 mg film-coated tablets* (round, red-colored, bi-convex tablets debossed with OC on one side and 60 on the other)
- 80 mg film-coated tablets* (round, green-colored, bi-convex tablets debossed with OC on one side and 80 on the other)

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

4 CONTRAINDICATIONS

OxyContin is 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
- Hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

OxyContin contains oxycodone, an opioid agonist and a Schedule II controlled substance. Oxycodone can be abused in a manner similar to other opioid agonists legal or illicit. 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 OxyContin in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is 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). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death *[see Overdosage (10)]*.

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

Respiratory depression is the chief hazard of opioid agonists, including OxyContin. Respiratory depression if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. 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)]*.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OxyContin, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with OxyContin and following dose increases. Instruct patients against use by individuals other than the patient for whom OxyContin was prescribed and to keep OxyContin out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of OxyContin are essential *[see Dosage and Administration (2)]*. Overestimating the OxyContin dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and OxyContin should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
- OxyContin 60 mg and 80 mg tablets are for use in opioid-tolerant patients only. Ingestion of these strengths of OxyContin tablets may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.
- Instruct patients to swallow OxyContin tablets intact. The tablets are not to be crushed, dissolved, or chewed. The resulting oxycodone dose may be fatal, particularly in opioid-naïve individuals.
- OxyContin is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression *[see Contraindications (4)]*.

5.3 Accidental Exposure

Accidental ingestion of OxyContin, especially in children, can result in a fatal overdose of oxycodone.

5.4 Elderly, Cachectic, and Debilitated Patients

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. Therefore, monitor such patients closely, particularly when initiating and titrating OxyContin and when OxyContin is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.5 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 OxyContin, as in these patients, even usual therapeutic doses of OxyContin 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.

5.6 Interactions with Alcohol, CNS Depressants, and Illicit Drugs

Hypotension, and profound sedation, coma or respiratory depression may result if OxyContin is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids). When considering the use of OxyContin 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, consider the patient's use, if any, of alcohol and/or illicit drugs that can cause CNS depression. If OxyContin therapy is to be initiated in a patient taking a CNS depressant, start with a lower OxyContin dose than usual and 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)]*.

5.7 Hypotensive Effects

OxyContin 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 OxyContin. In patients with circulatory shock, OxyContin may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OxyContin in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking OxyContin 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 OxyContin. OxyContin 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 OxyContin in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

OxyContin is contraindicated in patients with GI obstruction, including paralytic ileus. The oxycodone in OxyContin 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.

5.10 Use in Patients with Convulsive or Seizure Disorders

The oxycodone in OxyContin 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 OxyContin therapy.

5.11 Avoidance of Withdrawal

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

When discontinuing OxyContin, gradually taper the dose *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue OxyContin.

5.12 Driving and Operating Machinery

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

5.13 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, 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 OxyContin 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)]*.

5.14 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 adverse reactions described elsewhere in the labeling include:

- Respiratory depression *[see Boxed Warning, Warnings and Precautions (5.2, 5.5), and Overdosage (10)]*
- CNS depression *[see Drug Interactions (7.1), and Overdosage (10)]*
- Hypotensive effects *[see Warning and Precautions (5.7), and Overdosage (10)]*
- Drug abuse, addiction, and dependence *[see Drug Abuse and Dependence (9.2, 9.3)]*

- Gastrointestinal Effects *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*

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 OxyContin 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 OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OxyContin 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 OxyContin with placebo are shown in Table 1 below:

TABLE 1: Common Adverse Reactions (>5%)

Adverse Reaction	**OxyContin (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 OxyContin 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, 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 OxyContin. Advise patients how to recognize such a reaction and when to seek medical attention.

7 DRUG INTERACTIONS

7.1 CNS Depressants

Concurrent use of OxyContin and other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol can increase the risk of respiratory depression, hypotension, profound sedation or coma. Monitor patients receiving CNS depressants and OxyContin for signs of respiratory depression and hypotension. When such combined therapy is contemplated, start OxyContin at 1/3 to 1/2 of the usual dosage and consider using a lower dose of the concomitant CNS depressant.

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 OxyContin for signs of respiratory depression that may be greater than otherwise expected.

7.3 Agents Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4:

Co-administration of a strong CYP3A4 inhibitor ketoconazole, with OxyContin, significantly increased the plasma concentrations of oxycodone. 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 prolong opioid effects. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4:

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, significantly decreased plasma oxycodone concentrations. 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 with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inhibitors of CYP2D6:

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 during oxycodone treatment. However, clinicians should be aware of this possible interaction.

7.4 Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should generally not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as OxyContin. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients.

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 OxyContin is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. In animal reproduction and developmental toxicology studies, no evidence of fetal harm was observed. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.

Teratogenic Effects

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 2.0 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 and psycho-physiologic effects in neonates. OxyContin is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may 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.

Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate.

8.3 Nursing Mothers

Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OxyContin. Do not initiate OxyContin 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 OxyContin 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 OxyContin cautiously in these patients.

8.6 Hepatic Impairment

A study of OxyContin 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 OxyContin, 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.

8.9 Neonatal Opioid Withdrawal Syndrome

Chronic maternal use of oxycodone during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal 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 withdrawal syndrome vary based on the drug used, duration of use, the dose of last maternal use, and rate of elimination of drug by the newborn. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

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

9.2 Abuse

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

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 addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

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.

OxyContin, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping 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 OxyContin

OxyContin is for oral use only. Abuse of OxyContin poses a risk of overdose and death. This risk is increased with concurrent abuse of OxyContin with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of overdose and death.

Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

With parenteral abuse, the tablet excipients can result in death, 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.

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, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OxyContin should not be abruptly discontinued *[see Dosage and Administration (2.4)]*. If OxyContin is 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 (8.9)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with OxyContin 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.

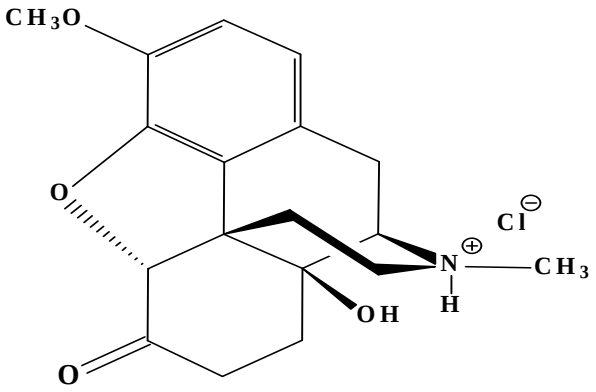
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on OxyContin. 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 OxyContin, carefully monitor the patient until spontaneous respiration is reliably reestablished. OxyContin 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

OxyContin (oxycodone hydrochloride controlled-release) is an opioid analgesic supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 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, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 15 mg tablets also contain black iron oxide, yellow iron oxide, and red iron oxide.

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

The 30 mg tablets also contain polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

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

The 60 mg tablets also contain polysorbate 80 and FD&C Red No. 40 Aluminum Lake

The 80 mg tablets also contain FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

OxyContin® 10 mg, 20 mg, 40 mg, and 80 mg Tablets are tested using USP Dissolution Test 2 and meet the associated tolerances provided in Acceptance Table 2 of the Oxycodone Hydrochloride Extended-Release Tablets USP Monograph.

OxyContin® 15 mg, 30 mg, and 60 mg Tablets are not described in the USP but are tested using USP Dissolution Test 2 of the Oxycodone Hydrochloride Extended-Release Tablets USP Monograph.

12 CLINICAL PHARMACOLOGY

Oxycodone is a pure mu receptor opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, hydrocodone and oxymorphone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Increasing doses of pure mu receptor agonists are associated with increasing analgesia. There is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by adverse reactions, the more serious of which may include somnolence and respiratory 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 OxyContin (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. OxyContin 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 OxyContin 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 OxyContin is primarily due to the parent drug oxycodone. OxyContin is designed to provide delivery of oxycodone over 12 hours.

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

Oxycodone release from OxyContin is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OxyContin to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OxyContin 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 OxyContin 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. In healthy subjects, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-lives of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 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 2 below*). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption

(AUC) (*see Table 3 below*). 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 OxyContin Tablets. In a study comparing 10 mg of OxyContin 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 2

Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

TABLE 3

Mean [% coefficient variation]

Regimen	Dosage Form	AUC_{∞} (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg OxyContin*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg OxyContin*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = $AUC_{0\text{-}inf}$; for multiple-dose AUC = $AUC_{0\text{-}T}$
* data obtained while volunteers received naltrexone, which can enhance absorption

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin.

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.

Special Populations

Elderly (≥ 65 years)

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 $t_{½}$ for oxycodone increased by 2.3 hours.

Drug-Drug Interactions

CYP3A4 Inhibitors

CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of OxyContin (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 OxyContin *[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, OxyContin 20 mg, but not 10 mg, was statistically significant in pain reduction compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

OxyContin (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-100-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 15 mg are round, unscored, gray-colored, convex tablets imprinted with OC on one side and 15 on the other. They are supplied as follows:

NDC 59011-815-10: child-resistant closure, opaque plastic bottles of 100

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-103-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 30 mg are round, unscored, brown-colored, convex tablets imprinted with OC on one side and 30 on the other. They are supplied as follows:

NDC 59011-830-10: child-resistant closure, opaque plastic bottles of 100

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-105-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 60 mg are round, unscored red-colored, convex tablets imprinted with OC on one side and 60 on the other. They are supplied as follows:

NDC 59011-860-10: child-resistant closure, opaque plastic bottles of 100

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-107-20: unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton
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

See FDA-approved patient labeling (Medication Guide)

Abuse Potential

Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.

Life-Threatening Respiratory Depression

Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting OxyContin or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Exposure

Instruct patients to take steps to store OxyContin securely. Accidental exposure, especially in children, may result in serious harm or death. Advise patients to dispose of unused OxyContin by flushing the tablets down the toilet.

Risks from Concomitant Use of Alcohol and other CNS Depressants

Inform patients that the concomitant use of alcohol with OxyContin can increase the risk of life-threatening respiratory depression. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter drug products that contain alcohol, during treatment with OxyContin.

Inform patients that potentially serious additive effects may occur if OxyContin is 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 OxyContin, including the following:

- OxyContin is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OxyContin tablets can result in a fatal overdose.

Hypotension

Inform patients that OxyContin 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 OxyContin 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 OxyContin. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that OxyContin can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

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Medication Guide

OXYCONTIN® (ox-e-KON-tin)
(oxycodone hydrochloride controlled-release) Tablets, CII

OXYCONTIN is:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain.

Important information about OXYCONTIN:
- Get emergency help right away if you take too much OXYCONTIN (overdose). OXYCONTIN overdose can cause life-threatening breathing problems that can lead to death.
- Never give anyone else your OXYCONTIN. They could die from taking it. Store OXYCONTIN away from children and in a safe place to prevent stealing or abuse. Selling or giving away OXYCONTIN is against the law.

Do not take OXYCONTIN if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking OXYCONTIN, 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.** OXYCONTIN may harm your unborn baby.
- **breastfeeding.** OXYCONTIN passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

When taking OXYCONTIN:
- Do not change your dose. Take OXYCONTIN exactly as prescribed by your healthcare provider.
- Take each dose every 12 hours at the same time every day. If you miss a dose, take OXYCONTIN as soon as possible and then take your next dose 12 hours later. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take more than 1 dose in 12 hours.
- Swallow OXYCONTIN whole. Do not cut, break, chew, crush, dissolve, or inject OXYCONTIN.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCONTIN without talking to your healthcare provider.**
- After you stop taking OXYCONTIN, flush any unused tablets down the toilet.

While taking OXYCONTIN Do Not:
- Drive or operate heavy machinery, until you know how OXYCONTIN affects you. OXYCONTIN can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of OXYCONTIN 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, or you are feeling faint.

These are not all the possible side effects of OXYCONTIN. 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**

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, **www.purduepharma.com or call 1-888-726-7535**

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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OxyContin® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS