

# PRIMLEV

Oxycodone HCl/Acetaminophen

Available in 5/300, 7.5/300 & 10/300 mg

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**Addiction, Abuse, and Misuse**  
**PRIMLEV™** exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing **PRIMLEV™**, and monitor all patients regularly for the development of these behaviors and conditions [see **WARNINGS**].

**Life-Threatening Respiratory Depression**  
Serious, life-threatening, or fatal respiratory depression may occur with use of **PRIMLEV™**. Monitor for respiratory depression, especially during initiation of **PRIMLEV™** or following a dose increase [see **WARNINGS**].

**Accidental Ingestion**  
Accidental ingestion of **PRIMLEV™**, especially by children, can result in a fatal overdose of **PRIMLEV™** [see **WARNINGS**].

**Neonatal Opioid Withdrawal Syndrome**  
Prolonged use of **PRIMLEV™** 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**].

**Cytochrome P450 3A4 Interaction**  
The concomitant use of **PRIMLEV™** with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving **PRIMLEV™** and any CYP3A4 inhibitor or inducer [see **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions**].

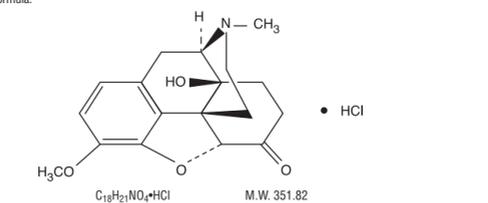
**Hepatotoxicity**  
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 mg per day, and often involve more than one acetaminophen-containing product.

**Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**  
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see **WARNINGS, PRECAUTIONS; Drug Interactions**].  
• Reserve concomitant prescribing of **PRIMLEV™** and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.  
• Limit dosages and durations to the minimum required.  
• Follow patients for signs and symptoms of respiratory depression and sedation.

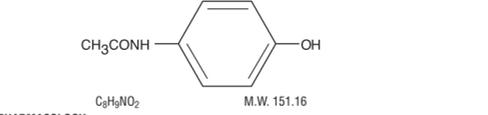
**DESCRIPTION**  
Oxycodone hydrochloride and acetaminophen are available in tablets for oral administration.  
Each **PRIMLEV™** 5 mg/300 mg contains:  
Oxycodone Hydrochloride USP..... 5 mg\*  
(\*5 mg Oxycodone Hydrochloride is equivalent to 4.4815 mg Oxycodone)  
Acetaminophen USP..... 300 mg  
Each **PRIMLEV™** 7.5 mg/300 mg contains:  
Oxycodone Hydrochloride USP..... 7.5 mg\*  
(\*7.5 mg Oxycodone Hydrochloride is equivalent to 6.7228 mg Oxycodone)  
Acetaminophen USP..... 300 mg  
Each **PRIMLEV™** 10 mg/300 mg contains:  
Oxycodone Hydrochloride USP..... 10 mg\*  
(\*10 mg Oxycodone Hydrochloride is equivalent to 8.9637 mg Oxycodone)  
Acetaminophen USP..... 300 mg

**Inactive Ingredients**  
The tablets contain: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid. In addition the 5 mg/300 mg strength contains D&C Yellow #1; the 7.5 mg/300 mg strength contains FD&C Red #40 Aluminum Lake; the 10 mg/300 mg strength contains FD&C Yellow #6 Aluminum Lake.

**PRIMLEV™** contains oxycodone, 14-hydroxydihydrocodeinone, a semisynthetic opioid analgesic which occurs as a white to off-white fine crystalline powder. The molecular formula for oxycodone hydrochloride is C<sub>18</sub>H<sub>27</sub>NO<sub>4</sub>·HCl and the molecular weight is 351.82. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



**PRIMLEV™** contains acetaminophen, 4'-hydroxyacetanilide, a non-opioid, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder. The molecular formula for acetaminophen is C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub> and the molecular weight is 151.16. It may be represented by the following structural formula:



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

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.  
The precise mechanism of the analgesic properties of acetaminophen is not established but is thought to involve central actions.

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

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

Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

**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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

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

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

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

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

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

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

**Pharmacokinetics**  
**Absorption and Distribution**  
The mean absolute oral bioavailability of oxycodone in cancer patients was reported to be about 87%. Oxycodone has been shown to be 45% bound to human plasma proteins *in vitro*. The volume of distribution after intravenous administration is 211.9 ±166.6 L.

Absorption of acetaminophen is rapid and almost complete from the GI tract after oral administration. With overdose, absorption is complete in 4 hours. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication.

**Metabolism and Elimination**  
**Oxycodone**  
In humans, oxycodone is extensively metabolized to noroxycodone by means of CYP3A-mediated N-demethylation, oxymorphone by means of CYP2D6-mediated O-demethylation, and their glucuronides [see **PRECAUTIONS; Drug Interactions**].

**Acetaminophen**  
Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. A small fraction (10-25%) of acetaminophen is bound to plasma proteins. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See **OVERDOSAGE** for toxicity information.

**INDICATIONS AND USAGE**  
**PRIMLEV™** (oxycodone and acetaminophen tablets, USP) is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

**Limitations of Use**  
Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see **WARNINGS**], reserve **PRIMLEV™** for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are not available or expected to be tolerated.  
• Have not been tolerated, or are not expected to be tolerated.  
• Have not provided adequate analgesia, or are not expected to provide adequate analgesia

**CONTRAINDICATIONS**  
**PRIMLEV™** is contraindicated in patients with:  
• Significant respiratory depression [see **WARNINGS**]  
• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see **WARNINGS**]  
• Known or suspected gastrointestinal obstruction, including paralytic ileus [see **WARNINGS**]  
• Hypersensitivity to oxycodone, acetaminophen, or any other component of the product (e.g., anaphylaxis) [see **WARNINGS, ADVERSE REACTIONS**]

**WARNINGS**  
**Addiction, Abuse, and Misuse**  
**PRIMLEV™** contains oxycodone, a Schedule II controlled substance. As an opioid, **PRIMLEV™** exposes users to the risks of addiction, abuse, and misuse [see **DRUG ABUSE AND DEPENDENCE**].

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

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing **PRIMLEV™**. 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 **PRECAUTIONS; Information for Patients/Caregivers**]. 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.

**Life-Threatening Respiratory Depression**  
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see **OVERDOSAGE**]. Carbon dioxide (CO<sub>2</sub>) 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 **PRIMLEV™**, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of **PRIMLEV™**.

To reduce the risk of respiratory depression, proper dosing and titration of **PRIMLEV™** is essential [see **DOSE AND ADMINISTRATION**]. Overestimating the **PRIMLEV™** dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.  
Accidental ingestion of **PRIMLEV™**, especially by children, can result in respiratory depression and death due to an overdose of **PRIMLEV™**.

**Neonatal Opioid Withdrawal Syndrome**  
Prolonged use of **PRIMLEV™** during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see **PRECAUTIONS; Information for Patients/Caregivers; Pregnancy**].

**Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers**  
Concomitant use of **PRIMLEV™** with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone hydrochloride and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see **WARNINGS**], particularly when an inhibitor is added after a stable dose of **PRIMLEV™** is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in **PRIMLEV™**-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using **PRIMLEV™** with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in **PRIMLEV™**-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of **PRIMLEV™** until stable drug effects are achieved [see **PRECAUTIONS; Drug Interactions**].

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

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

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

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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

**Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**  
The use of **PRIMLEV™** in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

**Patients with Chronic Pulmonary Disease:** **PRIMLEV™**-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of **PRIMLEV™** [see **WARNINGS; Life-Threatening Respiratory Depression**].

**Elderly, Cachectic, or Debilitated Patients:** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see **WARNINGS; Life-Threatening Respiratory Depression**].

Monitor such patients closely, particularly when initiating and titrating **PRIMLEV™** and when **PRIMLEV™** is given concomitantly with other drugs that depress respiration [see **WARNINGS; Life-Threatening Respiratory Depression**]. Alternatively, consider the use of non-opioid analgesics in these patients.

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

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

**Hepatotoxicity**  
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.

**Serious Skin Reactions**  
Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

**Hypersensitivity/Anaphylaxis**  
There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue **PRIMLEV™** immediately and seek medical care if they experience these symptoms. Do not prescribe **PRIMLEV™** for patients with acetaminophen allergy [see **PRECAUTIONS; Information for Patients/Caregivers**].

**Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**  
In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), **PRIMLEV™** may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with **PRIMLEV™**.

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

**Risks of Use in Patients with Gastrointestinal Conditions**  
**PRIMLEV™** is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The administration of **PRIMLEV™**, or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

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

**Increased Risk of Seizures in Patients with Seizure Disorders**  
The oxycodone in **PRIMLEV™** may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during **PRIMLEV™** therapy.

**Withdrawal**  
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including **PRIMLEV™**. In these patients, mixed agonist/antagonist and partial analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing **PRIMLEV™**, gradually taper the dosage [see **DOSE AND ADMINISTRATION**]. Do not abruptly discontinue **PRIMLEV™** [see **DRUG ABUSE AND DEPENDENCE**].

**Risks of Driving and Operating Machinery**  
**PRIMLEV™** may impair the mental and 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 **PRIMLEV™** and know how they will react to the medication [see **PRECAUTIONS; Information for Patients/Caregivers**].

**PRECAUTIONS**  
**Information for Patients/Caregivers**  
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Addiction, Abuse, and Misuse**  
Inform patients that the use of **PRIMLEV™**, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see **WARNINGS**]. Instruct patients not to share **PRIMLEV™** with others and to take steps to protect **PRIMLEV™** 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 **PRIMLEV™** or when the dosage is increased, and that it can occur even at recommended dosages [see **WARNINGS**]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

**Accidental Ingestion**  
Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see **WARNINGS**]. Instruct patients to take steps to store **PRIMLEV™** securely and to dispose of unused **PRIMLEV™** by flushing tablets down the toilet. In the case of accidental ingestions, emergency medical care should be sought immediately.

**Interactions with Benzodiazepines and Other CNS Depressants**  
Inform patients and caregivers that potentially fatal additive effects may occur if **PRIMLEV™** is used with benzodiazepines and other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see **WARNINGS, PRECAUTIONS; Drug Interactions**].

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

**Monamine Oxidase Inhibitor (MAOI) Interaction**  
Inform patients to avoid taking **PRIMLEV™** while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking **PRIMLEV™** [see **PRECAUTIONS; Drug Interactions**].

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

**Important Administration Instructions**  
Instruct patients how to properly take **PRIMLEV™** (see **DOSE AND ADMINISTRATION, WARNINGS**). Advise patients not to adjust the medication dose themselves and to consult with their healthcare provider prior to any dosage adjustment.

Advise patients who are treated with **PRIMLEV™** for more than a few weeks not to abruptly discontinue the medication. Advise patients to consult with their physician for a gradual discontinuation dose schedule to taper off the medication.

**Maximum Daily Dose of Acetaminophen**  
Inform patients not to take more than 4000 milligrams of acetaminophen per day. Advise patients to call their prescriber if they take more than the recommended dose.

**Hypotension**  
Inform patients that **PRIMLEV™** 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 such as hypotension or fainting (e.g., sit or lie down, carefully rise from a sitting or lying position) [see **WARNINGS**].

**Anaphylaxis**  
Inform patients that anaphylaxis has been reported with ingredients contained in **PRIMLEV™**. Advise patients how to recognize such a reaction and when to seek medical attention [see **CONTRAINDICATIONS, ADVERSE REACTIONS**].

**Pregnancy**  
**Neonatal Opioid Withdrawal Syndrome**  
Inform female patients of reproductive potential that prolonged use of **PRIMLEV™** during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see **WARNINGS, PRECAUTIONS; Pregnancy**].

**Embryo-Fetal Toxicity**  
Inform female patients of reproductive potential that **PRIMLEV™** can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [see **PRECAUTIONS; Pregnancy**].

**Lactation**  
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see **PRECAUTIONS; Nursing Mothers**].

**Fertility**  
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see **ADVERSE REACTIONS**].

**Driving or Operating Heavy Machinery**  
Inform patients that **PRIMLEV™** may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see **PRECAUTIONS**].

**Constipation**  
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see **ADVERSE REACTIONS, CLINICAL PHARMACOLOGY**].

**Disposal of Unused PRIMLEV™**  
Advise patients to dispose of unused **PRIMLEV™** by flushing unused tablets down the toilet.

**Laboratory Tests**  
Although oxycodone may cross-react with some drug urine tests, no available studies were found which determined the duration of detectability of oxycodone in urine drug screens. However, based on pharmacokinetic data, the approximate duration of detectability for a single dose of oxycodone is roughly estimated to be one to two days following drug exposure. Urine testing for opiates may be performed to determine illicit drug use and for medical reasons such as evaluation of patients with altered states of consciousness or monitoring efficacy of drug rehabilitation efforts. The preliminary identification of opiates in urine involves the use of an immunoassay screening and thin-layer chromatography (TLC). Gas chromatography/mass spectrometry (GC/MS) may be utilized as a third-stage identification step in the medical investigation process for opiate testing after immunoassay and TLC. The identities of 6-keto opiates (e.g., oxycodone) can further be differentiated by the analysis of their methoxymethylmethylsilyl (MO-TMS) derivative.

**Drug Interactions**  
**Inhibitors of CYP3A4 and CYP2D6**  
The concomitant use of **PRIMLEV™** and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of **PRIMLEV™** and CYP3A4 and CYP2D6 inhibitors, particularly when an inhibitor is added after a stable dose of **PRIMLEV™** is achieved [see **WARNINGS**].

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease [see **CLINICAL PHARMACOLOGY**], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to **PRIMLEV™**.

If concomitant use is necessary, consider dosage reduction of **PRIMLEV™** until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the **PRIMLEV™** dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

**Inducers of CYP3A4**  
The concomitant use of **PRIMLEV™** and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, can decrease the plasma concentration of oxycodone [see **CLINICAL PHARMACOLOGY**

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHD and greater (based on a body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

**Infertility**

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see **ADVERSE REACTIONS**].

**Pregnancy**

**Teratogenic Effects**

Animal reproductive studies have not been conducted with **PRIMLEV™**. It is also not known whether **PRIMLEV™** can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. **PRIMLEV™** should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

**Nonteratogenic Effects**

**Fetal/Neonatal Adverse Reactions**

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see **WARNINGS**].

**Labor or Delivery**

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

**Nursing Mothers**

Ordinarily, nursing should not be undertaken while a patient is receiving **PRIMLEV™** because of the possibility of sedation and/or respiratory depression in the infant. Oxycodone is excreted in breast milk in low concentrations, and there have been rare reports of somnolence and lethargy in babies of nursing mothers taking an oxycodone/acetaminophen product. Acetaminophen is also excreted in breast milk in low concentrations.

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

Infants exposed to **PRIMLEV™** through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

**Pediatric Use**

Safety and effectiveness of **PRIMLEV™** in pediatric patients have not been established.

**Geriatric Use**

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

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of **PRIMLEV™** slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see **WARNINGS**].

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

**Hepatic Impairment**

In a pharmacokinetic study of oxycodone in patients with end-stage liver disease, oxycodone plasma clearance decreased and the elimination half-life increased.

Because oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Initiate therapy in these patients with a lower than usual dosage of **PRIMLEV™** and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see **CLINICAL PHARMACOLOGY**].

**Renal Impairment**

In a study of patients with end stage renal impairment, mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Oxycodone should be used with caution in patients with renal impairment.

Because oxycodone is known to be substantially excreted by the kidney, its clearance may decrease in patients with renal impairment. Initiate therapy with a lower than usual dosage of **PRIMLEV™** and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see **CLINICAL PHARMACOLOGY**].

**ADVERSE REACTIONS**

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

Serious adverse reactions that may be associated with oxycodone and acetaminophen use include respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and shock [see **OVERDOSAGE**].

The most frequently observed non-serious adverse reactions include lightheadedness, dizziness, drowsiness or sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

Hypersensitivity reactions may include: Skin eruptions, urticarial, erythematous skin reactions. Hematologic reactions may include: thrombocytopenia, neutropenia, pancytopenia, hemolytic anemia. Rare cases of agranulocytosis have likewise been associated with acetaminophen use. In high doses, the most serious adverse effect is a dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma also may occur.

Other adverse reactions obtained from postmarketing experiences with oxycodone and acetaminophen are listed by organ system and in decreasing order of severity and/or frequency as follows:

**Body as a Whole:** Anaphylactoid reaction, allergic reaction, malaise, asthenia, fatigue, chest pain, fever, hypothermia, thirst, headache, increased sweating, accidental overdose, non-accidental overdose

**Cardiovascular:** Hypotension, hypertension, tachycardia, orthostatic hypotension, bradycardia, palpitations, dysrhythmias  
**Central and Peripheral Nervous System:** Stupor, tremor, paraesthesia, hypoesthesia, lethargy, seizures, anxiety, mental impairment, agitation, cerebral edema, confusion, dizziness

**Fluid and Electrolyte:** Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis

**Gastrointestinal:** Dyspepsia, taste disturbances, abdominal pain, abdominal distention, sweating increased, diarrhea, dry mouth, flatulence, gastro-intestinal disorder, nausea, vomiting, pancreatitis, intestinal obstruction, ileus

**Hepatic:** Transient elevations of hepatic enzymes, increase in bilirubin, hepatitis, hepatic failure, jaundice, hepatotoxicity, hepatic disorder

**Hearing and Vestibular:** Hearing loss, tinnitus

**Hematologic:** Thrombocytopenia

**Hypersensitivity:** Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria, anaphylactoid reaction

**Metabolic and Nutritional:** Hypoglycemia, hyperglycemia, acidosis, alkalosis

**Musculoskeletal:** Myalgia, rhabdomyolysis

**Ocular:** Miosis, visual disturbances, red eye

**Psychiatric:** Drug dependence, drug abuse, insomnia, confusion, anxiety, agitation, depressed level of consciousness, nervousness, hallucination, somnolence, depression, suicide

**Respiratory System:** Bronchospasm, dyspnea, hyperpnea, pulmonary edema, tachypnea, aspiration, hypoventilation, laryngeal edema

**Skin and Appendages:** Erythema, urticaria, rash, flushing

**Urogenital:** Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure, urinary retention

- **Serotonin syndrome:** Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
- **Adrenal insufficiency:** Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- **Anaphylaxis:** Anaphylaxis has been reported with ingredients contained in **PRIMLEV™**.
- **Androgen deficiency:** Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

**DRUG ABUSE AND DEPENDENCE**

**Controlled Substance**

**PRIMLEV™** contains oxycodone, a Schedule II controlled substance.

**Abuse**

**PRIMLEV™** contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, oxycodone, and tapentadol. **PRIMLEV™** can be abused and is subject to misuse, addiction, and criminal diversion [see **WARNINGS**].

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

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

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

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers 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.

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

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

**Risks Specific to Abuse of PRIMLEV™**

**PRIMLEV™** is for oral use only. Abuse of **PRIMLEV™** poses a risk of overdose and death. The risk is increased with concurrent abuse of **PRIMLEV™** with alcohol and other central nervous system depressants.

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

**Dependence**

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

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

**PRIMLEV™** should not be abruptly discontinued in a physically-dependent patient [see **DOSE AND ADMINISTRATION**]. If **PRIMLEV™** is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, 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 **PRECAUTIONS: Pregnancy**].

**OVERDOSAGE**

Following an acute overdose, toxicity may result from the oxycodone or the acetaminophen.

**Clinical Presentation**

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

**Acetaminophen**

Dose-dependent potentially fatal hepatic necrosis is the most serious adverse effect of acetaminophen overdose. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

**Treatment of Overdose**

**Oxycodone**

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 and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

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

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

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

**Acetaminophen**

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

**DOESAGE AND ADMINISTRATION**

**Important Dosage and Administration Instructions**

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see **WARNINGS**].

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see **WARNINGS**]. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with **PRIMLEV™** and adjust the dosage accordingly [see **WARNINGS**].

**Initial Dosage**

**Initiating Treatment with PRIMLEV™**

The usual adult dosage is as follows. The total daily dose of acetaminophen should not exceed 4 grams.

Strength	Usual Adult Dosage	Maximal Daily Dose
5 mg/300 mg	1 tablet every 6 hours as needed for pain	12 Tablets
7.5 mg/300 mg	1 tablet every 6 hours as needed for pain	8 Tablets
10 mg/300 mg	1 tablet every 6 hours as needed for pain	6 Tablets

**Conversion from PRIMLEV™ to Extended-Release Oxycodone**

The relative bioavailability of **PRIMLEV™** compared to extended-release oxycodone is unknown, so conversion to extended-release oxycodone must be accompanied by close observation for signs of excessive sedation and respiratory depression.

**Titration and Maintenance of Therapy**

Individually titrate **PRIMLEV™** to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving **PRIMLEV™** to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see **WARNINGS**]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the **PRIMLEV™** dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

**Discontinuation of PRIMLEV™**

When a patient who has been taking **PRIMLEV™** regularly and may be physically dependent no longer requires therapy with **PRIMLEV™**, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop **PRIMLEV™** abruptly [see **WARNINGS, DRUG ABUSE AND DEPENDENCE**].

**HOW SUPPLIED**

**PRIMLEV™** (oxycodone and acetaminophen tablets, USP) is supplied as follows:

**PRIMLEV™ 5 mg/300 mg**  
Yellow, capsule-shaped, convex face tablets, debossed "A" score "P" on one side and "681" on the other side.

Bottles of 100 tablets NDC# 24090-681-88

**PRIMLEV™ 7.5 mg/300 mg**  
Red, capsule-shaped, flat face, beveled edge tablets, debossed "A P" on one side and "682" on the other side.

Bottles of 100 tablets NDC# 24090-682-88

**PRIMLEV™ 10 mg/300 mg**  
Orange, oval-shaped, convex face tablets, debossed "A P" on one side and "683" on the other side.

Bottles of 100 tablets NDC# 24090-683-88

**Storage**

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure (as required).

For further product information, please visit [www.akrimax.com](http://www.akrimax.com) or call our medical communications department toll-free at 1-888-383-1733.



Manufactured for Akrimax Pharmaceuticals, LLC, Cranford, NJ 07016  
By MIKART, INC., Atlanta, GA 30318  
Marketed and Distributed by:  
Akrimax Pharmaceuticals, LLC  
Cranford, NJ 07016

<b>MEDICATION GUIDE</b> <b>PRIMLEV™</b> (prim'lev) <b>Oxycodone and Acetaminophen Tablets, CII</b>	
<b>PRIMLEV™ is:</b> <ul style="list-style-type: none"> <li>• A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate and when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.</li> <li>• An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.</li> </ul>	
<b>Important information about PRIMLEV™:</b> <ul style="list-style-type: none"> <li>• <b>Get emergency help right away if you take too much PRIMLEV™ (overdose).</b> When you first start taking <b>PRIMLEV™</b>, 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. Taking <b>PRIMLEV™</b> with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.</li> <li>• Never give anyone else your <b>PRIMLEV™</b>. They could die from taking it. Store <b>PRIMLEV™</b> away from children and in a safe place to prevent stealing or abuse. Selling or giving away <b>PRIMLEV™</b> is against the law.</li> </ul>	
<b>Do not take PRIMLEV™ if you have:</b> <ul style="list-style-type: none"> <li>• Severe asthma, trouble breathing, or other lung problems</li> <li>• A bowel blockage or have narrowing of the stomach or intestines</li> <li>• Known hypersensitivity to oxycodone, acetaminophen, or any ingredient in <b>PRIMLEV™</b></li> </ul>	
<b>Before taking PRIMLEV™, tell your healthcare provider if you have a history of:</b> <ul style="list-style-type: none"> <li>• Head injury, seizures</li> <li>• Liver, kidney, thyroid problems</li> <li>• Problems urinating</li> <li>• Pancreas or gallbladder problems</li> <li>• Abuse of street or prescription drugs, alcohol addiction, or mental health problems</li> </ul>	
<b>Tell your healthcare provider if you are:</b> <ul style="list-style-type: none"> <li>• <b>Pregnant or planning to become pregnant.</b> Prolonged use of <b>PRIMLEV™</b> during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.</li> <li>• <b>Breastfeeding.</b> <b>PRIMLEV™</b> passes into breast milk and may harm your baby.</li> <li>• Taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking <b>PRIMLEV™</b> with certain other medicines can cause serious side effects that could lead to death.</li> </ul>	
<b>When taking PRIMLEV™:</b> <ul style="list-style-type: none"> <li>• Do not change your dose. Take <b>PRIMLEV™</b> exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.</li> <li>• Take your prescribed dose every 6 hours as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.</li> <li>• Call your healthcare provider if the dose you are taking does not control your pain.</li> <li>• If you have been taking <b>PRIMLEV™</b> regularly, do not stop taking <b>PRIMLEV™</b> without talking to your healthcare provider.</li> <li>• After you stop taking <b>PRIMLEV™</b>, dispose of unused tablets by flushing them down the toilet.</li> </ul>	
<b>While taking PRIMLEV™ DO NOT:</b> <ul style="list-style-type: none"> <li>• Drive or operate heavy machinery, until you know how <b>PRIMLEV™</b> affects you. <b>PRIMLEV™</b> can make you sleepy, dizzy, or lightheaded.</li> <li>• Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with <b>PRIMLEV™</b> may cause you to overdose and die.</li> </ul>	
<b>The possible side effects of PRIMLEV™:</b> <ul style="list-style-type: none"> <li>• Constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.</li> </ul>	
<b>Get emergency medical help if you have:</b> <ul style="list-style-type: none"> <li>• Trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.</li> </ul>	
These are not all the possible side effects of <b>PRIMLEV™</b> . 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 <a href="http://dailymed.nlm.nih.gov">dailymed.nlm.nih.gov</a>	
This Medication Guide has been approved by the U.S. Food and Drug Administration.	
Issued: 07/2017 Code 1143A00 368F105	