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| PERCOCET® (Oxycodone and Acetaminophen Tablets, USP) |
| <div> <div>CII</div> <div>Rx only</div> </div> |

Revised: August 2020

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOOTOXICITY, AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

PERCOCET 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 PERCOCET, and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of PERCOCET. Monitor for respiratory depression, especially during initiation of PERCOCET or following a dose increase [see WARNINGS].

Accidental Ingestion

Accidental ingestion of PERCOCET, especially by children, can result in a fatal overdose of PERCOCET [see WARNINGS].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PERCOCET 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 PERCOCET 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 concentrations. Monitor patients receiving PERCOCET 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 PERCOCET 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

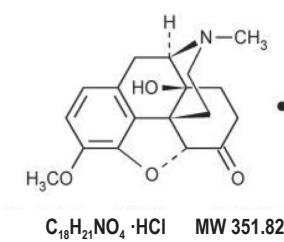
Oxycodone Hydrochloride and Acetaminophen is available in tablets for oral administration.

Each tablet for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:

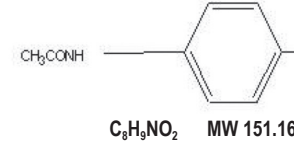
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|---|---------|
| Oxycodone Hydrochloride, USP | 2.5 mg |
| (2.5 mg oxycodone hydrochloride is equivalent to 2.2409 mg of oxycodone.) | |
| Acetaminophen, USP | 325 mg |
| Oxycodone Hydrochloride, USP | 5 mg* |
| (5 mg oxycodone hydrochloride is equivalent to 4.4815 mg of oxycodone.) | |
| Acetaminophen, USP | 325 mg |
| Oxycodone Hydrochloride, USP | 7.5 mg* |
| (7.5 mg oxycodone hydrochloride is equivalent to 6.7228 mg of oxycodone.) | |
| Acetaminophen, USP | 325 mg |
| Oxycodone Hydrochloride, USP | 10 mg* |
| (10 mg oxycodone hydrochloride is equivalent to 8.9637 mg of oxycodone.) | |
| Acetaminophen, USP | 325 mg |

All strengths of PERCOCET also contain the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, microcrystalline cellulose, polyvinylpyrrolidone, and stearic acid. May also contain opiate. In addition, the 2.5 mg/325 mg strength contains FD&C Red No. 40 Aluminum Lake and the 5 mg/325 mg strength contains FD&C Blue No. 1 Aluminum Lake. The 7.5 mg/325 mg strength contains FD&C Yellow No. 6 Aluminum Lake. The 10 mg/325 mg strength contains D&C Yellow No. 10 Aluminum Lake. The 5 mg/325 mg strength and the 10 mg/325 mg strength may also contain corn starch.

Oxycodone Hydrochloride and Acetaminophen Tablets contain oxycodone, 14-hydroxydihydrocodeine, a semisynthetic opioid analgesic which occurs as a white to off-white fine crystalline powder. The molecular formula for oxycodone hydrochloride is C₁₈H₂₁NO₄·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:



Oxycodone Hydrochloride and Acetaminophen Tablets contain acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder. The molecular formula for acetaminophen is C₉H₉NO₂ 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 precise therapeutic action of oxycodone is analgesic. Like all full opioid agonists, there is no ceiling effect for analgesia with oxycodone.

Clinical, dosagely 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 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 in 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 opioid agonists. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see DOSAGE AND ADMINISTRATION].

Concentration-Adverse Reaction Relationships

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

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 ±186.6 L.

Absorption of acetaminophen is rapid and almost complete from the GI tract after oral administration. With overdose, acetaminophen is rapidly absorbed and 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, oxycodone 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 to 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 renal impairment. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of conjugates. Acetaminophen is 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

PERCOCET is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative therapy is inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see WARNINGS], reserve PERCOCET for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]

- 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

PERCOCET 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

PERCOCET contains oxycodone, a Schedule II controlled substance. As an opioid, PERCOCET 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 be incurred in patients appropriately prescribed PERCOCET. 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 PERCOCET, and monitor all patients regularly 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 PERCOCET, but use in such patients necessitates intensive counseling about the risks and proper use of PERCOCET along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS, Life-Threatening Respiratory Depression; DOSAGE AND ADMINISTRATION, Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing PERCOCET. 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].

Obtain informed consent from patients or their caregivers, local state professional licensing board, or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMS2012.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS OMECE, call 800-503-0784, or go to www.fda.gov/OpioidAnalgesicREMS2012. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMS2012print.

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. Monitor patients and their caregivers closely for signs of respiratory depression, including decreased or absent respirations, depending on the patient's clinical status [see OVERDOSAGE]. Carbon dioxide (CO₂) 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 PERCOCET, 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 PERCOCET. To reduce the risk of respiratory depression, proper dosing and titration of PERCOCET are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the PERCOCET dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see PRECAUTIONS, Information for Patients/Caregivers].

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

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

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

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of other CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see WARNINGS, Addiction, Abuse, and Misuse, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants; PRECAUTIONS, Information for Patients/Caregivers].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PERCOCET 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 PERCOCET 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 PERCOCET is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in PERCOCET-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using PERCOCET with CYP3A4 inhibitors, discontinuing CYP3A4 inducers in PERCOCET-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of PERCOCET until stable drug effects are achieved [see PRECAUTIONS; Drug Interactions].

Concomitant use of PERCOCET with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone hydrochloride plasma concentrations and decrease its analgesic effect. In patients with withdrawal syndrome in a patient who had developed physical dependence to oxycodone hydrochloride. When using PERCOCET 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

Concomitant use of PERCOCET with benzodiazepines or other CNS depressants may increase the risks of respiratory depression, coma, and death may result from concomitant use of PERCOCET 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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see WARNINGS, Life-Threatening Respiratory Depression; DOSAGE AND ADMINISTRATION, Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose].

Advise both patients and caregivers about the risks of respiratory depression and sedation when PERCOCET 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. Soreen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk of 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 PERCOCET 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: PERCOCET-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 PERCOCET [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 PERCOCET and when PERCOCET 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. Warn the patient 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

PERCOCET 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; Information for Patients/Caregivers]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of PERCOCET. In patients with circulatory shock PERCOCET may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of PERCOCET 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 the 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 PERCOCET immediately and seek medical care if they experience these symptoms. Do not prescribe PERCOCET 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 CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), PERCOCET may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with PERCOCET.

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

Risks of Use in Patients with Gastrointestinal Conditions

PERCOCET are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The administration of PERCOCET, or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

The oxycodone in PERCOCET 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 PERCOCET 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 PERCOCET therapy.

Withdrawal

Do not abruptly discontinue PERCOCET in a patient physically dependent on opioids. When discontinuing PERCOCET in a physically dependent patient, gradually taper

Pregnancy
Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of PERCOCET 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 PERCOCET 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 impress. Instruct nursing mothers to seek immediate medical care if they notice these signs [see **PRECAUTIONS, Nursing Mothers**].

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

Driving or Operating Heavy Machinery
Inform patients that PERCOCET may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform task 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**].

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 investigational sequence 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 methoxymethylmethanoyl (NMO-TMS) derivative.

Drug Interactions
Inhibitors of CYP3A4 and CYP2D6
The concomitant use of PERCOCET 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 PERCOCET and CYP3A4 and CYP2D6 inhibitors, particularly when an inhibitor is added after a stable dose of PERCOCET 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 PERCOCET.
If concomitant use is necessary, consider dosage reduction of PERCOCET 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 PERCOCET dosage until stable drug effects are achieved.
Monitor for signs of opioid withdrawal.

Inducers of CYP3A4
The concomitant use of PERCOCET and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, can decrease the plasma concentration of oxycodone [see **CLINICAL PHARMACOLOGY**], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to PERCOCET [see **WARNINGS**].
After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase [see **CLINICAL PHARMACOLOGY**], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
If concomitant use is necessary, consider increasing the PERCOCET dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider PERCOCET dosage reduction and monitor for signs of respiratory depression.

Benzodiazepines and Other CNS Depressants
Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants such as benzodiazepines and other sedative hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see **WARNINGS**].

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tryptans, 5-HT₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), central muscle relaxants (metaxalone, metaxalone), and monoamine oxidase (MAO) inhibitors (other than used to treat psychiatric disorders and also others, such as linezolid and intravenous methylglucamine blue), has resulted in serotonin syndrome. [see **PRECAUTIONS, Information for Patients/Caregivers**].
If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue PERCOCET if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs)
The concomitant use of opioids and MAOIs, such as phenelzine, tranylcypromine, linezolid, may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see **WARNINGS**].
The use of PERCOCET is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
The concomitant use of opioids with other opioid analgesics, such as buprenorphine, nalbuphine, pentazocine, may reduce the analgesic effect of PERCOCET and/or precipitate withdrawal symptoms.
Advise patient to avoid concomitant use of these drugs.

Muscle Relaxants
PERCOCET may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increase in the degree of respiratory depression.
If concomitant use is warranted, monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of PERCOCET and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose [see **WARNINGS**].

Diuretics
Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
If concomitant use is warranted, monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs
The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
If concomitant use is warranted, monitor patients for signs of urinary retention or reduced gastric motility when PERCOCET is used concomitantly with anticholinergic drugs.

Alcohol, Abuse
Hepatotoxicity has occurred in chronic alcoholics following various dose levels (moderate to excessive) of acetaminophen.

Oral Contraceptives
Increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of acetaminophen.

Charcoal (activated)
Reduces acetaminophen absorption when administered as soon as possible after overdose.

Beta-Blockers (Propranolol)
Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of acetaminophen. Therefore, the pharmacologic effects of acetaminophen may be increased.

Loop Diuretics
The effects of loop diuretic may be decreased because acetaminophen may decrease renal prostaglandin excretion and decrease plasma renal activity.

Lamotrigine
Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects.

Probenecid
Probenecid may increase the therapeutic effectiveness of acetaminophen slightly.

Zidovudine
The pharmacologic effects of zidovudine may be decreased because of enhanced non-hepatic or renal clearance of zidovudine.

Drug/Laboratory Test Interactions
Depending on the sensitivity/specificity and the test methodology, the individual components of PERCOCET may cross-react with assays used in the preliminary detection of cocaine (primary urinary metabolite, benzoylecgonine) or marijuana (cannabinoids) in human urine. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. The preferred confirmatory method is gas chromatography/mass spectrometry (GC/MS). Moreover, clinical considerations and professional judgment should be applied to any drug-of-abuse test result, particularly when preliminary positive results are used.
Acetaminophen may interfere with home blood glucose measurement systems; decreases of >20% in mean glucose values may be noted. This effect appears to be drug, concentration and system dependent.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term studies to evaluate the carcinogenic potential of the combination of Oxycodone Hydrochloride and Acetaminophen have not been conducted.
Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F₁ mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times the maximum daily dose (up to 1.2 to 1.4 times the MHDD, based on a body surface area comparison).
Mutagenesis
The combination of Oxycodone Hydrochloride and Acetaminophen has not been evaluated for mutagenicity. Oxycodone alone was negative in a bacterial reverse mutation assay (Ames), an *in vitro* chromosome aberration assay with human lymphocytes without metabolic activation and an *in vivo* mouse micronucleus assay. Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation and in the mouse lymphoma assay with or without metabolic activation.
In the published literature, acetaminophen has been reported to be clastogenic when administered at 1500 mg/kg/day to the rat model (3.5-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.
Impairment of Fertility
In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.72 times the MHDD (based on a body surface area comparison). There was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.
Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface comparison) resulted 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
Pregnancy Category C
Animal reproductive studies have not been conducted with PERCOCET. It is also not known whether PERCOCET can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. PERCOCET 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-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. PERCOCET is opioid antagonist that may be used in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including PERCOCET, 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 PERCOCET 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 PERCOCET and any potential adverse effects on the breastfed infant from PERCOCET or from the underlying medical condition.
Infants exposed to PERCOCET 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 PERCOCET in pediatric patients have not been established.

Geriatric Use
Elderly patients (aged 65 years or older) may have increased sensitivity PERCOCET. 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 PERCOCET 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 of renal impairment may be substantially increased 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 PERCOCET 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 PERCOCET 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 PERCOCET. Because these reactions are reported' following use 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, sleepiness 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: Shunt, tremor, paraesthesia, hypoaesthesia, 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, gastrointestinal discomfort, 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 PERCOCET.
- **Androgen deficiency:** Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

DRUG ABUSE AND DEPENDENCE
Controlled Substance
PERCOCET contains oxycodone, a Schedule II controlled substance.

Abuse
PERCOCET contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and tapentadol. PERCOCET 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. Precaution 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.
PERCOCET, 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 opioids.

Risks Specific to Abuse of PERCOCET
PERCOCET is for oral use only. Abuse of PERCOCET poses a risk of overdose and death. The risk is increased with concurrent abuse of PERCOCET 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 is a physiological state in which the body adapts to the drug after a period of regular exposures, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, buprenorphine, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until several days to weeks of continued opioid usage.
Do not abruptly discontinue PERCOCET in a patient physically dependent on opioids. Rapid tapering of PERCOCET in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid

discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

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

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 overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, 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.
Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist. Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in PERCOCET, 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. In severe 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.

DOSEAGE 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 PERCOCET and adjust the dosage accordingly [see **WARNINGS**].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose
Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with PERCOCET [see **WARNINGS, Life-Threatening Respiratory Depression; PRECAUTIONS, Information for Patients/Caregivers**]. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing regulations (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [see **WARNINGS, Addiction, Abuse, and Misuse, Life-Threatening Respiratory Depression, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**].

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

Initial Dosage
Initiating Treatment with PERCOCET
Initiate treatment with PERCOCET **Tablets 2.5 mg/325 mg** adult dosage, with one or 2 tablets every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams.
The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams.

| Strength | Usual Adult Dosage | Maximal Daily Dose |
|------------------------|---|--------------------|
| PERCOCET 2.5 mg/325 mg | 1 or 2 tablets every 6 hours as needed for pain | 12 Tablets |
| PERCOCET 5 mg/325 mg | 1 tablet every 6 hours as needed for pain | 12 Tablets |
| PERCOCET 7.5 mg/325 mg | 1 tablet every 6 hours as needed for pain | 8 Tablets |
| PERCOCET 10 mg/325 mg | 1 tablet every 6 hours as needed for pain | 6 Tablets |

Conversion from Oxycodone Hydrochloride and Acetaminophen to Extended-Release Oxycodone
The relative bioavailability of Oxycodone Hydrochloride and Acetaminophen Tablets or Oral Solution 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 PERCOCET to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving PERCOCET 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 PERCOCET 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.

Safe Reduction or Discontinuation of Oxycodone Hydrochloride and Acetaminophen Tablets and Oral Solution
Do not abruptly discontinue PERCOCET in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.
When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking PERCOCET, there are a variety of factors that should be considered, including the dose of PERCOCET the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.
There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on PERCOCET who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.
It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.
When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [see **WARNINGS/ Withdrawal, DRUG ABUSE AND DEPENDENCE**].

HOW SUPPLIED
PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is supplied as follows:
2.5 mg/325 mg
Pink, oval, tablet, debossed with "PERCOCET" on one side and "2.5" on the other.
Bottles of 100 NDC 63481-627-70
5 mg/325 mg
Blue, round, tablet, debossed with "PERCOCET" and "5" on one side and bisect on the other.
Bottles of 100 NDC 63481-623-70
7.5 mg/325 mg
Peach, oval-shaped, tablet, debossed with "PERCOCET" on one side and "7.5/325" on the other.
Bottles of 100 NDC 63481-628-70
10 mg/325 mg
Yellow, capsule-shaped, tablet, debossed with "PERCOCET" on one side and "10/325" on the other.
Bottles of 100 NDC 63481-629-70

Storage
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from moisture. Dispense in a light, light-resistant container as defined in the USP.
Store PERCOCET securely and dispose of properly [see **PRECAUTIONS/Information for Patients**].
DEA Order Form Required.

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Par Pharmaceutical
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