PERCODAN®

(Oxycodone and Aspirin Tablets, USP)

CII

Rx only

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

Addiction, Abuse, and Misuse

PERCODAN 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 PERCODAN 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 PERCODAN. Monitor for respiratory depression, especially during initiation of PERCODAN or following a dose increase (see WARNINGS).

Accidental Ingestion

Accidental ingestion of even one dose of PERCODAN, especially by children, can result in a fatal overdose of oxycodone (see WARNINGS).

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PERCODAN 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 PERCODAN 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 PERCODAN and any CYP3A4 inhibitor or inducer (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions).

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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)

- **Reserve concomitant prescribing of PERCODAN 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

PERCODAN (oxycodone HCl USP and aspirin USP) tablets are an immediate-release opioid agonist intended for oral administration only.

Each PERCODAN Tablet contains:

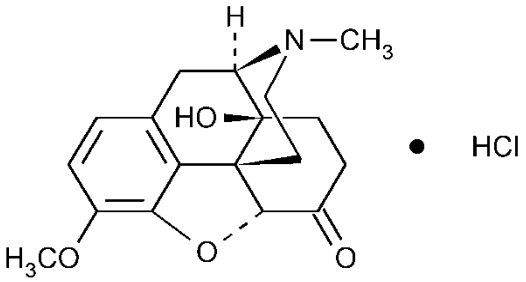
Oxycodone Hydrochloride, USP 4.8355 mg*

Aspirin, USP 325 mg

*4.8355 mg oxycodone HCl is equivalent to 4.3346 mg of oxycodone as the free base.

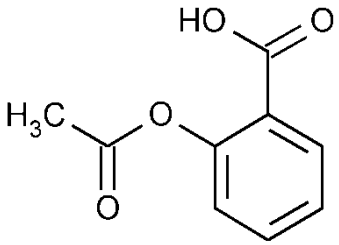
PERCODAN Tablets also contain the following inactive ingredients: D&C Yellow 10, FD&C Yellow 6, microcrystalline cellulose and corn starch.

The oxycodone hydrochloride component is Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)-., a white to off-white, hygroscopic crystals or powder, odorless, soluble in water; slightly soluble in alcohol and is represented by the following structural formula:



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

The aspirin component is 2-(acetyloxy)-, Benzoic acid, a white crystal, commonly tabular or needle-like, or white, crystalline powder. Is odorless or has a faint odor. Is stable in dry air; in moist air it gradually hydrolyzes to salicylic and acetic acids. Slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether; sparingly soluble in absolute ether and is represented by the following structural formula:



$C_9H_8O_4$ MW 180.16

CLINICAL PHARMACOLOGY

Mechanism of Action

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

The precise mechanism of the analgesic action of oxycodone 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.

Aspirin (acetylsalicylic acid) works by inhibiting the body's production of prostaglandins, including prostaglandins involved in inflammation. Prostaglandins cause pain sensations by stimulating muscle contractions and dilating blood vessels throughout the body. In the CNS, aspirin works on the hypothalamus heat-regulating center to reduce fever, however, other mechanisms may be involved.

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 increases in both carbon dioxide tension and electrical stimulation.

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

Effects on 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.

Aspirin can produce gastrointestinal injury (lesions, ulcers) through a mechanism that is not yet completely understood, but may involve a reduction in eicosanoid synthesis by the gastric mucosa. Decreased production of prostaglandins may compromise the defenses of the gastric mucosa and the activity of substances involved in tissue repair and ulcer healing.

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 and sweating and/or orthostatic hypotension.

Use caution in hypovolemic patients, such as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

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 low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date (see ADVERSE REACTIONS).

Effects on the Immune System

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

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with 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 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).

The dose of PERCODAN must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients (see DOSAGE AND ADMINISTRATION).

Platelet Aggregation

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin 12 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

Pharmacokinetics

Absorption

The mean absolute oral bioavailability of oxycodone in cancer patients was reported to be about 87%. This high oral bioavailability is due to low pre-systemic elimination and/or first-pass metabolism.

Distribution

The volume of distribution after intravenous administration is 211.9 ±186.6 L. Oxycodone has been shown to be 45% bound to human plasma proteins *in vitro*. Oxycodone has been found in breast milk (see PRECAUTIONS).

Aspirin is hydrolyzed primarily to salicylic acid in the gut wall and during first-pass metabolism through the liver. Salicylic acid is absorbed rapidly from the stomach, but most of the absorption occurs in the proximal small intestine. Following absorption, salicylate is distributed to most body tissues and fluids, including fetal tissues, breast milk, and the CNS. High concentrations are found in the liver and kidneys. Salicylate is variably bound to serum proteins, particularly albumin.

Elimination

Metabolism

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

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

The biotransformation of aspirin occurs primarily in the liver by the microsomal enzyme system. With a plasma half-life of approximately 15 minutes, aspirin is rapidly hydrolyzed to salicylate. At low doses, salicylate elimination follows first-order kinetics. The plasma half-life of salicylate is approximately 2 to 3 hours.

Excretion

Free and conjugated noroxycodone, free and conjugated oxycodone, and oxymorphone are excreted in human urine following a single oral dose of oxycodone. Approximately 8% to 14% of the dose is excreted as free oxycodone over 24 hours after administration.

Approximately 10% of aspirin is excreted as unchanged salicylate in the urine. The major metabolites excreted in the urine are salicyluric acid (75%), salicyl phenolic glucuronide (10%), salicyl acyl glucuronide (5%), and gentisic and gentisuric acid (less than 1%) each. Eighty to 100% of a single dose is excreted in the urine within 24 to 72 hours.

Drug-Drug Interactions (see PRECAUTIONS)

Inhibitors of CYP3A4

Since the CYP3A4 isoenzyme plays a major role in the metabolism of PERCODAN, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and C_{max} by 3.6 and 1.7 fold, respectively. The expected clinical results would be increased or prolonged opioid effects.

Inducers of CYP450

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and C_{max} by 86% and 63% respectively. The expected clinical results would be lack of efficacy or, possibly, development of abstinence syndrome

in a patient who had developed physical dependence to oxycodone. Induction of CYP3A4 may be of greatest importance given oxycodone's metabolic pathways.

INDICATIONS AND USAGE

PERCODAN 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 PERCODAN 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

PERCODAN 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 or aspirin, (e.g. angioedema) (see WARNINGS)
- Patients with hemophilia.
- Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome (see WARNINGS)

WARNINGS

Addiction, Abuse, and Misuse

PERCODAN contain Oxycodone, a Schedule II controlled substance. As an opioid, PERCODAN 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 PERCODAN. 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 PERCODAN, and monitor all patients receiving PERCODAN 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 PERCODAN, but use in such patients necessitates intensive counseling about the risks and proper use of PERCODAN 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 PERCODAN. 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). 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_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of PERCODAN, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of PERCODAN.

To reduce the risk of respiratory depression, proper dosing and titration of PERCODAN are essential (see DOSAGE AND ADMINISTRATION). Overestimating the PERCODAN 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 PERCODAN, especially by children can result in respiratory depression and death due to an overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PERCODAN 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, Pregnancy).

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

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

Concomitant use of PERCODAN with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using PERCODAN 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 PERCODAN 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 PERCODAN is used with benzodiazepine 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 (see PRECAUTIONS; Drug Interactions).

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

The use of PERCODAN 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: PERCODAN-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 PERCODAN (see WARNINGS).

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).

Monitor such patients closely, particularly when initiating and titrating PERCODAN and when PERCODAN is given concomitantly with other drugs that depress respiration (see WARNINGS). 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 1 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

PERCODAN 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). Monitor these patients for signs of hypotension after initiating or titrating the dosage of PERCODAN. In patients with circulatory shock, PERCODAN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of PERCODAN in patients with circulatory shock.

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), PERCODAN may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with PERCODAN.

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

Risks of Use in Patients with Gastrointestinal Conditions

PERCODAN is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxycodone in PERCODAN 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 PERCODAN 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 PERCODAN therapy.

Withdrawal

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

When discontinuing PERCODAN, gradually taper the dosage (see DOSAGE AND ADMINISTRATION. Do not abruptly discontinue PERCODAN (see DRUG ABUSE AND DEPENDENCE).

Risks of Driving and Operating Machinery

PERCODAN may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of PERCODAN and know how they will react to the medication (See PRECAUTIONS: Information for patients).

Hypersensitivity to Oxycodone or Aspirin, (e.g. angioedema)

PERCODAN tablets are contraindicated in patients with known hypersensitivity to oxycodone or aspirin, and in any situation where opioids or aspirin are contraindicated.

Reye Syndrome

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome with concomitant use of aspirin in certain viral illnesses

Alcohol Warning

Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

Peptic Ulcer Disease

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PRECAUTIONS

General

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Hemorrhage

Aspirin may increase the likelihood of hemorrhage due to its effect on the gastric mucosa and platelet function (prolongation of bleeding time). Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

Ambulatory Surgery and Postoperative Use

Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with use of opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

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 PERCODAN, 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 PERCODAN with others and to take steps to protect PERCODAN 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 PERCODAN 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 PERCODAN securely and to dispose of unused PERCODAN by flushing down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if PERCODAN is used with benzodiazepines or 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 PERCODAN 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 physicians if they are taking, or plan to take serotonergic medications.

MAOI Interaction

Inform patients to avoid taking PERCODAN while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking PERCODAN (see PRECAUTIONS; Drug Interactions).

Adrenal Insufficiency

Inform patients that PERCODAN 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 PERCODAN. The usual dosage is one tablet every 6 hours as needed for pain. The maximum daily dose of aspirin should not exceed 4 grams (see DOSAGE AND ADMINISTRATION, and PRECAUTIONS)

Hypotension

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

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in PERCODAN. 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 PERCODAN 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 PERCODAN 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.

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 PERCODAN 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 WARNINGS).

Constipation

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

Disposal of Unused PERCODAN

Advise patients to dispose of unused PERCODAN by flushing the tablets down the toilet or disposing of in accordance with local guidelines and/or regulations.

.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 methoxime-trimethylsilyl (MO-TMS) derivative.

Table 1: Clinically Significant Drug Interactions with PERCODAN

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of PERCODAN and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of PERCODAN and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of PERCODAN 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 oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of PERCODAN 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 PERCODAN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of PERCODAN and CYP3A4 inducers 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 oxycodone (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.
Intervention: *Examples:*	If concomitant use is necessary, consider increasing the PERCODAN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider PERCODAN dosage reduction and monitor for signs of respiratory depression. Rifampin, carbamazepine, phenytoin
Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see WARNINGS).
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue PERCODAN if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) (see WARNINGS).
Intervention:	The use of PERCODAN 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.
Examples	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of PERCODAN and/or precipitate withdrawal symptoms
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine,
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of PERCODAN and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when PERCODAN is used concomitantly with anticholinergic drugs.

Analgesics	
Clinical Impact:	Analgesics may reduce the analgesic effect of oxycodone or may precipitate withdrawal symptoms
Intervention:	Should be administered with caution to a patient who has received or is receiving a full opioid agonist such as oxycodone.
Examples:	pentazocine, nalbuphine, naltrexone, and butorphanol

Drug/Drug Interactions with Aspirin

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Aspirin may enhance the serious side and toxicity of methotrexate due to displacement from its plasma protein binding sites and/or reduced renal clearance.

Nonsteroidal Anti-inflammatory Drugs (NSAID's): The concurrent use of aspirin with other NSAID's should be avoided because this may increase bleeding or lead to decreased renal function. Aspirin may enhance the serious side effects and toxicity of ketorolac, due to displacement from its plasma protein binding sites and/or reduced renal clearance.

Oral Hypoglycemics Agents: Aspirin may increase the serum glucose-lowering action of insulin and sulfonylureas leading to hypoglycemia.

Uricosuric Agents: Salicylates antagonize the uricosuric action of probenecid or sulfinpyrazone.

Drug/Laboratory Test Interactions

Depending on the sensitivity/specificity and the test methodology, the individual components of PERCODAN tablets 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.

Salicylates may increase the protein bound iodine (PBI) result by competing for the protein binding sites on pre-albumin and possibly thyroid-binding globulins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

The combination of oxycodone and aspirin 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. Aspirin induced chromosome aberrations in cultured human fibroblasts.

Impairment of Fertility

Animal studies to evaluate the effects of oxycodone on fertility have not been conducted. Aspirin has been shown to inhibit ovulation in rats.

Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome (see WARNINGS). Available data with PERCODAN are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Reproduction studies in rats and rabbits demonstrated that oral administration of oxycodone was not teratogenic or embryo-fetal toxic. In several published studies, treatment of pregnant rats with oxycodone at clinically relevant doses and below, resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2-4% and 14-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions:

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal 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 pyscho-physiologic effects in neonates. An opioid antagonist, such as naloxone must be available for reversal of opioid-induced respiratory depression in the neonate. PERCODAN is not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics, including

PERCODAN, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Salicylates readily cross the placenta and by inhibiting prostaglandin synthesis, may cause constriction of ductus arteriosus resulting in pulmonary hypertension and increased fetal mortality and, possibly other untoward fetal effects. Aspirin use in pregnancy can also result in alteration in maternal and neonatal hemostasis mechanisms. Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence of intracranial hemorrhage in premature infants, stillbirths and neonatal death. Use during pregnancy, especially in the third trimester, should be avoided.

Data

Animal Data

Reproduction studies in rats and rabbits demonstrated that oral administration of oxycodone was not teratogenic or embryo-fetal toxic. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit neurobehavioral effects including altered stress responses, increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3-times an adult human dose of 60 mg/day, on a mg/m^2 basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human dose of 60 mg/day, on a mg/m^2 basis).

Lactation

Risk Summary

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended-release oxycodone, including PERCODAN, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with PERCODAN.

Salicylic acid has been detected in breast milk. Adverse effects on platelet function in the nursing infant exposed to aspiring in breast milk may be a potential risk. Furthermore, the risk of Reye Syndrome cause by salicylate in breast milk is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PERCODAN and any potential adverse effects on the breastfed child from PERCODAN or from the underlying maternal condition.

Clinical Considerations

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

Females and Males of Reproductive Potential

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.

Pediatric Use

PERCODAN tablets should not be administered to pediatric patients. Reye Syndrome is a rare but serious disease which can follow flu or chicken pox in children and teenagers. While the cause of Reye Syndrome is unknown, some reports claim aspirin (or salicylates) may increase the risk of developing this disease.

Geriatric Use

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

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

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. 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. Care should be exercised when oxycodone is used in patients with hepatic impairment.

Avoid aspirin in patients with severe hepatic impairment.

Renal Impairment

In a study of patients with end stage renal impairment, mean elimination half-life of oxycodone 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.

Avoid aspirin in patients with severe renal impairment (glomerular filtration rate less than 10 mL/minute).

ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse (see WARNINGS)
- Life-Threatening Respiratory Depression (see WARNINGS)
- Neonatal Opioid Withdrawal Syndrome (see WARNINGS)
- Interactions with Benzodiazepines and Other CNS Depressants (see WARNINGS)Adrenal Insufficiency (see WARNINGS)
- Severe Hypotension (see WARNINGS)
- Gastrointestinal Adverse Reactions (see WARNINGS)
- Seizures (see WARNINGS)
- Withdrawal (see WARNINGS)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Serious adverse reactions that may be associated with PERCODAN tablet use include, apnea, circulatory depression, hypotension, respiratory arrest, respiratory depression, 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.

Aspirin may increase the likelihood of hemorrhage due to its effect on the gastric mucosa and platelet function. Furthermore, aspirin has the potential to cause anaphylaxis in hypersensitive patients as well as angioedema especially in patients with chronic urticaria. Other adverse reactions due to aspirin use include anorexia, reversible hepatotoxicity, leukopenia, thrombocytopenia, purpura, decreased plasma iron concentration, and shortened erythrocyte survival time.

Postmarketing Experience

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

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

Body as a Whole

allergic reaction, malaise, asthenia, headache, anaphylaxis, fever, hypothermia, thirst, increased sweating, accident, accidental overdose, non-accidental overdose.

Cardiovascular

tachycardia, dysrhythmias, hypotension, orthostatic hypotension, bradycardia, palpitations

Central and Peripheral Nervous System

stupor, paresthesia, agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures, anxiety, mental impairment

Fluid and Electrolyte

dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis

Gastrointestinal

hemorrhagic gastric/duodenal ulcer, gastric/peptic ulcer, dyspepsia, abdominal pain, diarrhea, eructation, dry mouth, gastrointestinal bleeding, intestinal perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye syndrome, pancreatitis, intestinal obstruction, ileus

Hearing and Vestibular

hearing loss, tinnitus. Patients with high frequency loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Hematologic
unspecified hemorrhage, purpura, reticulocytosis, prolongation of prothrombin time, disseminated intravascular coagulation, ecchymosis, thrombocytopenia

Hypersensitivity

acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria, anaphylactoid reaction

Metabolic and Nutritional

hypoglycemia, hyperglycemia, acidosis, alkalosis

Musculoskeletal

rhabdomyolysis

Ocular

miosis, visual disturbances, red eye

Psychiatric

drug dependence, drug abuse, somnolence, depression, nervousness, hallucination

Reproductive

prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding, closure of patent ductus arteriosis

Respiratory System

bronchospasm, dyspnea, hyperpnea, pulmonary edema, tachypnea, aspiration, hypoventilation, laryngeal edema

Skin and Appendages

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 PERCODAN.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids (see CLINICAL PHARMACOLOGY).

OVERDOSAGE

Clinical Presentation

Acute overdose with PERCODAN 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.

Early signs of acute aspirin (salicylate) overdose including tinnitus occur at plasma concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are toxic. Severe toxic effects are associated with levels above 400 mcg/mL. A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately.

In acute salicylate overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration, and coma. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis. Serious symptoms such as depression, coma, and respiratory failure progress rapidly.

Salicylism (chronic salicylate toxicity) may be noted by symptoms such as dizziness, tinnitus, difficulty hearing, nausea, vomiting, diarrhea, and mental confusion. More severe salicylism may result in respiratory alkalosis.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen 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 PERCODAN overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to PERCODAN overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in PERCODAN, carefully monitor the patient until spontaneous respiration is reliably re-established. 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 begun with care and by titration with smaller than usual doses of the antagonist.

DOSAGE 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 24-72 hours of initiating therapy and following dosage increases with PERCODAN tablets and adjust the dosage accordingly (see WARNINGS).

Initial Dosage

Initiating Treatment with PERCODAN

Initiate treatment with one tablet every 6 hours as needed for pain. The maximum daily dose of aspirin should not exceed 4 grams or 12 tablets.

Titration and Maintenance of Therapy

Individually titrate PERCODAN to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving PERCODAN 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 PERCODAN 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 PERCODAN tablets

When a patient who has been taking PERCODAN regularly and may be physically dependent no longer requires therapy with PERCODAN, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue PERCODAN in a physically-dependent patient (see WARNINGS, DRUG ABUSE AND DEPENDENCE).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

PERCODAN contain oxycodone, a Schedule II controlled substance.

Abuse

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

PERCODAN 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 PERCODAN

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

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 through 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.

PERCODAN should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION). If PERCODAN 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).

HOW SUPPLIED

PERCODAN (Oxycodone and Aspirin Tablets, USP), tablets are supplied as a yellow round tablet, scored and debossed with “PERCODAN” on one side and plain on the other side.

Available in:
Bottles of 100 NDC 63481-121-70

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

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Medication Guide

PERCODAN® (ˈpər-kə-ˌdan) (oxycodone hydrochloride and aspirin) tablets, for oral use, CII

PERCODAN is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid pain medicine when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about PERCODAN:

- **Get emergency help right away if you take too much PERCODAN (overdose)**. When you first start taking PERCODAN, 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 PERCODAN with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your PERCODAN. They could die from taking it. Store PERCODAN away from children and in a safe place to prevent stealing or abuse. Selling or giving away PERCODAN is against the law.

Do not take PERCODAN if you have:

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

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

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

Tell your healthcare provider if you are:

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

When taking PERCODAN:

- Do not change your dose. Take PERCODAN exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed. Take your prescribed dose at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking PERCODAN regularly, do not stop taking PERCODAN without talking to your healthcare provider.
- After you stop taking PERCODAN, flush any unused tablets down the toilet.

While taking PERCODAN DO NOT:

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

The possible side effects of PERCODAN:

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

Get emergency medical help if you have:

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

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

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