LORTAB®
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
Rx Only

DESCRIPTION
LORTAB is supplied in tablet form for oral administration. Hydrocodone bitartrate is an opioid agonist and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4α,5α-epoxy-3-methyl-17β-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

\[\text{C}_{18}\text{H}_{21}\text{NO}_{4}\text{·H}_{2}\text{O} \quad \text{M.W.} = 341.38\]

Acetaminophen, 4'-hydroxyacetanilide, is a slightly bitter, white, odorless, crystalline powder, a non-steroidal, non-opioid analgesic and antipyretic. It has the following structural formula:

\[\text{C}_{8}\text{H}_{9}\text{N}_{2}\text{O}_{2} \quad \text{M.W.} = 151.16\]

Each LORTAB for oral administration are available in the following strengths.

<table>
<thead>
<tr>
<th>Product Strength</th>
<th>Hydrocodone Bitartrate</th>
<th>Acetaminophen</th>
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<tbody>
<tr>
<td>7.5 mg/325 mg</td>
<td>7.5 mg</td>
<td>325 mg</td>
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In addition each tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, silicon dioxide, and stearic acid.

Micro USP Dissolution Test 2.

CLINICAL PHARMACOLOGY
Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism of action is not known. Although it is related to the existence of opioid receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

CLINICAL PHARMACOLOGY
Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opioid receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism of action is not yet understood. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthesis. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems, however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.0 ± 5.6 ng/mL. Maximum serum levels were achieved at 1.5 ± 0.2 hours and the half-life was determined to be 3.6 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-dealkylation, N-oxidation, O-glucuronidation and O-sulfation to the corresponding 6- and 6-hydroxy-metabolites. See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is extensively metabolized in the liver. The plasma half-life in the 1–2.5 to 3.5 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is primarily by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration. In the glomerular catabolism with small amounts of other conjugates and unchanged drug. See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE
LORTAB (hydrocodone bitartrate and acetaminophen tablets) are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS
LORTAB tablets should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.

WARNINGS
Nasal Decongestion: 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 the majority of acetaminophen containing products contain equal or greater amounts of acetaminophen. An increased incidence of acute liver failure 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 acetaminophen-induced disseminated intravascular coagulopathy (AIDIC), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hepatotoxicity/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, and vomiting. There were inconsistent reports of the-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue LORTAB immediately and seek medical care if they experience these symptoms. Do not prescribe LORTAB for patients with acetaminophen allergy.

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to reduce cerebral blood flow may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Miosis, Abuse, and Diversion of Opioids: LORTAB contains hydrocodone, an opioid agonist, and is a schedule II controlled substance. Opioid products are habit forming and are subject to diversion. Hydrocodone, like all narcotics, may impair the mentation and/or physical abilities required for driving a car or operating machinery; patients should be cautioned accordingly.

Drug Interactions: Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Information for Patients/Caregivers:
- Do not take LORTAB if you are allergic to any of its ingredients.
- If you develop signs of allergy such as a rash or difficulty breathing stop taking LORTAB and contact your healthcare provider immediately.
- Do not take more than 4000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.

Hydrocodone, like all narcotics, may impair the mentation and/or physical abilities required for driving a car or operating machinery; patients should be cautioned accordingly.

Patients receiving other narcotic analgesics, antihistamines, anti- pyretics, antipsychotics, anxiolytic agents, or other CNS depressants (including alcohol) concomitantly are more susceptible to the respiratory depressant effects of narcotics. Hence, when a patient receiving other CNS depressant agents is crossed over to another CNS depressant, the dose of one or both agents should be reduced.

Drug Interactions: Patients receiving other narcotic analgesics, antihistamines, anti- pyretics, antipsychotics, anxiolytic agents, or other CNS depressants (including alcohol) concomitantly with LORTAB may be at a greater risk of adverse CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the anticholinergic or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 3-8 hydroxydibutynine and 6-OH-acetaminophen.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenicity, mutagenicity, or impairment of fertility.

Preparations: Teratogenic Effects: Preparations Category C: There are no adequate and wel-controlled studies in pregnant women. LORTAB should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Narcotism/Inebriation: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The timeline of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.
Laker and Delivery: As with all narcotics, administration of LORTAB to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing, discontinue the drug, or otherwise adjust nursing and drug therapy.

Pediatric Use: Safety and effectiveness in the pediatric patients have not been established.

Geriatric Use: Clinical studies of LORTAB (hydrocodone bitartrate 5 mg and acetaminophen 500 mg) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosage selection for an elderly patient should be cautious, with dose selection being based on age, physical performance, mental performance, anemia, fever, dehydration, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of LORTAB may produce constipation.

Contraindications: Urticaria, sway of visual perception and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting on the brain stem respiratory center. Special Senses: Cases of hearing impairment or permanent loss have been reported predominantly in patients with chronic overdose.

Dermatological: Skin rash, pruritus.

The following adverse drug events may be seen in mind as potential effects of hydrocodone: allergic reactions, rash, urticaria, angioedema, anaphylaxis. Potential effects of high dosage are listed in the OVERDOSE section.

Drug Abuse and Dependence

Misuse, Abuse, and Dimension of Opioids: LORTAB contains hydrocodone, an opioid agonist, and is a Schedule II controlled substance. LORTAB, and other opioids used in analgesia can be abused and are subject to clinical diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable, relapsing disease utilizing a multidisciplinary approach, but relapse is common.

“Drug seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, refusal “loss” of prescriptions; threatening with prescription restrictions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physical dependence usually assumes clinically significant dimensions only after several weeks of continued opioid use, although a mild degree of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasing large doses are required to produce the same degree of analgesia, is manifest initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The role of development of tolerance varies among patients. Physicians should be aware that abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. LORTAB, like other opioids, may be diverted for non-medical use. Record keeping of prescriptions, including frequency, quantity, and renewal requests 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.

OVERDOSE

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

Signs and Symptoms

Hydrocodone: Severe overdose with hydrocodone is characterized by respiratory depression (decrease in respiratory rate and/or tidal volume), Cheyne-Stokes respiration, cyanosis, posturing, extremiti es rigorously progressing to spastic or convulsions, skeletal muscle rigidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, opia ne, coma, hypotension, cardio-renal, cardio-respiratory, and death may occur.

Acetaminophen: In overdose situations, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Rhabdomyolysis, hypoglycemic coma, and hepatic failure and death in infants may also occur. Serious symptoms in reversing a potentially hepatotoxic overdose may include nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48-72 hours post-ingestion.

Treatment: A single or multiple drug overdose with hydrocodone and acetaminophen is a potentially lethal poisoning event, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiovascular function and measures to reduce drug absorption. Oxygen, endotracheal intubation, and other supportive measures should be employed as indicated. Assist or controlled ventilation should also be considered.

For hydrocodone overdose, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antagonist against respiratory depression which may result from overdose or unusual sensitivity to narcotics, including hydrocodone. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continual surveillance, and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Gastric decontamination with activated charcoal should be administered (as prior to naloxone/ naltrindole (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity. Acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration with 0.3 g/kg.

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

DOSAGE AND ADMINISTRATION

Doseage should be adjusted according to the severity of the pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage for Hydrocodone Bitartrate and Acetaminophen Tablets USP is:

Product

Usual Adult

Dosage

(Abbreviated)

The total daily dosage

is not to exceed


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<tr>
<th>Product Description</th>
<th>Usual Adult Dosage</th>
<th>The total daily dosage is not to exceed</th>
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<tbody>
<tr>
<td>5 mg/325 mg</td>
<td>One or two tablets every four to six hours</td>
<td>12 tablets</td>
</tr>
<tr>
<td>7.5 mg/325 mg</td>
<td>One tablet every four to six hours</td>
<td>6 tablets</td>
</tr>
<tr>
<td>10 mg/325 mg</td>
<td>One tablet every four to six hours</td>
<td>6 tablets</td>
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HOW SUPPLIED

Each LORTAB® 5/325 tablet (hydrocodone bitartrate and acetaminophen tablets, USP: 5 mg/325 mg) contains hydrocodone bitartrate 5 mg and acetaminophen 325 mg. They are available as white capsule-shaped tablets, blunted on one side and debossed on the other side with 0 386.

DNC #6474-901-50

Bottles of 100

Bottles of 500

Each LORTAB® 7.5/325 tablet (hydrocodone bitartrate and acetaminophen tablets, USP: 7.5 mg/325 mg) contains hydrocodone bitartrate 7.5 mg and acetaminophen 325 mg. They are available as white capsule-shaped tablets, blunted on one side and debossed on the other side with 0 386.

DNC #6474-901-50

Bottles of 100

Bottles of 500

Each LORTAB® 10/325 tablet (hydrocodone bitartrate and acetaminophen tablets, USP: 10 mg/325 mg) contains hydrocodone bitartrate 10 mg and acetaminophen 325 mg. They are available as white capsule-shaped tablets, blunted on one side and debossed on the other side with 0 387.

DNC #6474-902-50

Bottles of 100

Bottles of 500

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

Dispense in a tight, light-resistant container with a child-resistant closure.

A Schedule II controlled drug substance.

Manufactured for:

UCB, Inc.

Smyrna, Georgia 30080

Lortab® is a registered trademark of the UCB Group of companies.

Manufactured by:

Teva Pharma, Inc.

Monmouth Junction, NJ 08852

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