

Extendryl® HC (guaifenesin and hydrocodone bitartrate)

Extended Release Tablet

Patent Pending

Rx Only

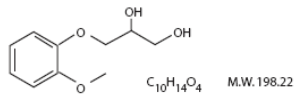
DESCRIPTION:

Each extended release tablet contains:

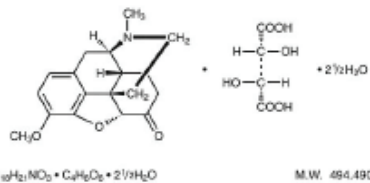
Guaifenesin.....1000 mg

Hydrocodone Bitartrate.....10 mg

Extendryl HC Tablets also contain the following inactive ingredients: Croscarmellose Sodium, Magnesium Stearate, Hydroxypropyl Methylcellulose, Silicon Dioxide and Microcrystalline Cellulose.



Guaifenesin is an expectorant. Chemically it is 3-(2-methoxyphenoxy)-1,2-propanediol, having the structural formula above:



Hydrocodone bitartrate is an opioid analgesic and antitussive. Chemically, it is 4,5(α)-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5), having the structural formula above:

CLINICAL PHARMACOLOGY:

Guaifenesin is an expectorant which increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of the cough reflex and of ciliary action in removing accumulated secretions from the trachea and bronchi. Guaifenesin is readily absorbed from the gastrointestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of one hour. The major urinary metabolite is β-(2-methoxyphenoxy) lactic acid. Hydrocodone bitartrate is an effective antitussive agent which is pharmacologically 2 to 8 times as potent as codeine and its sedative action is greater than codeine. The precise mechanism of action of hydrocodone and other opiates is not known, however, hydrocodone is believed to act by directly depressing the cough center. In excessive doses hydrocodone, like other opium derivatives, can depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system is insignificant. The constipation effects of hydrocodone are much weaker than that of morphine and no stronger than that of codeine. Hydrocodone can produce miosis, euphoria, physical and psychological dependence. At therapeutic antitussive doses, it does exert analgesic effects. Following a 10 mg oral dose of hydrocodone administered to five male human subjects, the mean peak concentration was 23.6 ± 5.2 mg/ml. Maximum serum levels were achieved at 1.3 ± 0.3 hours and half-life was determined to be 3.8 ± 0.3 hours.

INDICATIONS AND USAGE:

Extendryl® HC Tablets are indicated for the symptomatic relief of irritating non-productive cough associated with upper and lower respiratory tract congestion.

CONTRAINDICATIONS:

Extendryl® HC Tablets are contraindicated in individuals with known hypersensitivity to hydrocodone. Patients known to be hypersensitive to other opiates may exhibit cross-sensitivity to hydrocodone. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure; and wherever ventilatory function is depressed.

Warnings: May be habit forming. Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Extendryl® HC Tablets and they should be prescribed and administered with the same degree of caution appropriate to the use of other opioid drugs (See **DRUG ABUSE AND DEPENDENCE**).

PRECAUTIONS

General: DO NOT CRUSH OR CHEW EXTENDRYL HC TABLETS BEFORE INGESTION TO PRESERVE THE LONG-ACTING EFFECT.

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. 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.

Drug Interactions: Patients receiving other narcotic analgesics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with Extendryl HC Tablets may exhibit an additive 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 antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Drug/Laboratory Test Interactions: Guaifenesin interferes with the colorimetric determination of 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA). Administration of the drug should be discontinued 48 hours prior to the collection of urine specimens for such tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no animal or in vitro studies on the combination product guaifenesin and hydrocodone to evaluate carcinogenesis, mutagenesis, and impairment of fertility.

Pregnancy: Pregnancy Category C: Teratogenic Effects: There are no adequate and well-controlled studies in pregnant women. Extendryl® HC Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: 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 intensity 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.

Nursing Mothers: It is not known if guaifenesin is excreted in human milk. 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 6 years have not been established.

Geriatric Use: In general, dose selection for an elderly patient should be cautious, 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 drug therapy. Hydrocodone may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of hydrocodone bitartrate tablets and observed closely.

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 elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting 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.

ADVERSE REACTIONS:

Respiratory System: Hydrocodone produces dose-related respiratory depression by acting directly on brain stem respiratory centers.

Cardiovascular System: Hypertension, postural hypotension, tachycardia, and palpitations.

Genitourinary System: Ureteral spasm, spasm of vesicle sphincters and urinary retention have been reported with opiates.

Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, and blurred vision.

Gastrointestinal System: Nausea and vomiting occur more frequently in ambulatory than in recumbent patients

DRUG ABUSE AND DEPENDENCE:

Special care should be exercised in prescribing hydrocodone for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. Extendryl® HC is a Schedule III opioid. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of opioids; therefore, Extendryl HC Tablets should always be prescribed and administered with caution. Physical dependence is the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome. Patients physically dependent on opioids will develop an abstinence syndrome upon abrupt discontinuation of the opioid or following the administration of a opioid antagonist. The character and severity of the withdrawal symptoms are related to the degree of physical dependence. Manifestations of opioid withdrawal are similar to but milder than that of morphine and include lacrimation, rhinorrhea, yawning, sweating, restlessness, dilated pupils, anorexia, gooseflesh, irritability and tremor. In more severe forms, nausea, vomiting, intestinal spasm and diarrhea, increased heart rate and blood pressure, chills, and pains in bones and muscles of the back and extremities may occur. Peak effects will usually be apparent at 48 to 72 hours. Treatment of withdrawal is usually managed by providing sufficient quantities of an opioid to suppress severe withdrawal symptoms and then gradually reducing the dose of opioid over a period of several days.

OVERDOSAGE:

Since the effects of Extendryl® HC Tablets may last up to 12 hours, treatment of overdosage directed towards supporting the patient and reversing the effects of the drug should be continued for at least that length of time.

Saline cathartics may be useful in hastening the evacuation of unreleased medication.

Signs and symptoms: Overdosage of guaifenesin is unlikely to produce toxic effects since its toxicity is low. Guaifenesin, when administered by stomach tube to test animals in doses up to 5 gm/kg, produced no signs of toxicity. Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: A single or multiple overdose with hydrocodone is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous 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.