



HYCOTUSS®
(Hydrocodone bitartrate and Guaifenesin)
Expectorant Syrup

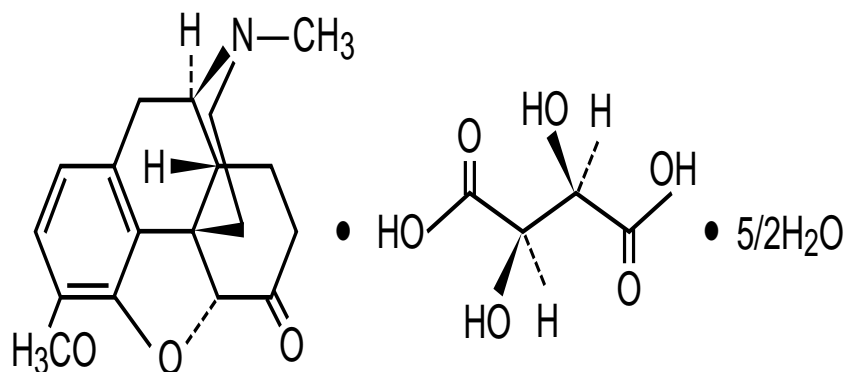
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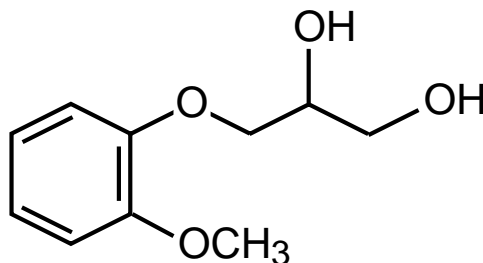
DESCRIPTION

HYCOTUSS (hydrocodone bitartrate and guaifenesin) Expectorant Syrup contains hydrocodone (dihydrocodeinone) bitartrate, a semi-synthetic centrally-acting opioid antitussive and guaifenesin, an expectorant for oral administration.

Chemically, Hydrocodone Bitartrate is 4, 5 α -epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1) hydrate (2:5) with the following structure:



Chemically, Guaifenesin is 3-(*o*-methoxyphenoxy)-1, 2-propanediol with the following structure:



Each teaspoonful (5 mL) contains:

Hydrocodone bitartrate, USP	5 mg
Guaifenesin, USP	100 mg
Alcohol, USP 1	0% v/v

Inactive Ingredients: FD&C Red No. 40, FD&C Yellow No. 6 (Sunset Yellow), flavoring, glycerin, methylparaben, propylparaben, purified water, sodium saccharin, sorbitol solution, and sucrose.

CLINICAL PHARMACOLOGY

Clinical trials have proven hydrocodone bitartrate to be an effective antitussive agent which is pharmacologically 2 to 8 times as potent as codeine. At equi-effective doses, 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 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and a half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

The exact mechanism of action is not established, but guaifenesin is believed to act by stimulating receptors in the gastric mucosa that initiate a reflex secretion of respiratory tract fluid, thereby increasing the volume and decreasing the viscosity of bronchial secretions. Studies with guaifenesin indicate that it is rapidly absorbed from the gastrointestinal tract and has a half-life of one hour.

INDICATIONS AND USAGE

HYCOTUSS Expectorant Syrup is indicated for the symptomatic relief of irritating non-productive cough associated with upper and lower respiratory tract congestion.

CONTRAINDICATIONS

HYCOTUSS Expectorant Syrup is contraindicated in patients hypersensitive to hydrocodone or guaifenesin. Patients known to be hypersensitive to other opioids may exhibit cross sensitivity to HYCOTUSS Expectorant Syrup. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure; and whenever 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 HYCOTUSS Expectorant Syrup and it should be prescribed and administered with the same degree of caution appropriate to the use of other opioid drugs (See DRUG ABUSE AND DEPENDENCE).

Respiratory Depression: HYCOTUSS Expectorant Syrup produces dose-related respiratory depression by directly acting on the brain stem respiratory centers. If respiratory depression occurs, it may be antagonized by the use of NARCAN® (naloxone hydrochloride) and other supportive measures when indicated.

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

Acute Abdominal Conditions: The administration of HYCOTUSS Expectorant Syrup or other opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

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.

Usage in Ambulatory Patients: Hydrocodone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, and patients should be warned accordingly.

Drug Interactions: Patients receiving other opioids, analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced (see WARNINGS).

Laboratory Interactions: The metabolite of guaifenesin has been found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaifenesin therefore may interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. Guaifenesin administration should be discontinued 24 hours prior to the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and reproduction studies have not been conducted with HYCOTUSS Expectorant Syrup.

Usage in Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with HYCOTUSS Expectorant Syrup. It is also not known whether HYCOTUSS Expectorant Syrup can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. HYCOTUSS Expectorant Syrup should be given to a pregnant woman only if clearly needed.

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. Chlorpromazine 0.7-1.0 mg/kg q 6 h, phenobarbital 2 mg/kg q 6 h, and paregoric 2-4 drops/kg q 4 h, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosages decreased as tolerated.

Nursing Mothers: It is not known whether this drug 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 HYCOTUSS Expectorant Syrup, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

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

Cardiovascular System: Hypertension, postural hypotension and palpitations.

Genitourinary System: Ureteral spasm, spasm of vesical 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.

HYCOTUSS Expectorant Syrup is a Schedule III opioid. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of opioids; therefore, HYCOTUSS Expectorant Syrup 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

Signs and Symptoms: Serious overdosage with HYCOTUSS Expectorant Syrup 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: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone

hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. Activated charcoal may be of benefit.

DOSAGE AND ADMINISTRATION

Usual Adult Dose: One teaspoonful (5 mL) after meals and at bedtime, not less than 4 hours apart (not to exceed 6 teaspoonfuls in a 24 hour period). Treatment should be initiated with one teaspoonful and subsequent doses, up to a maximum single dose of 3 teaspoonfuls, adjusted if required.

Usual Children's Dose:

Over 12 years: Initial dose 1 teaspoonful; maximum single dose, 2 teaspoonfuls.

6 to 12 years: Initial dose 1/2 teaspoonful; maximum single dose, 1 teaspoonful.

HOW SUPPLIED

HYCOTUSS (hydrocodone bitartrate and guaifenesin) Expectorant Syrup is available as an orange-colored, butterscotch flavored syrup in bottles as follows:

16 fl oz (473 mL)

NDC 63481-235-16

Store at controlled room temperature between 20°-25°C (68°-77°F). [See USP] Store and dispense in a tight, light-resistant container as described in the U.S.P.

Manufactured for:



Endo Pharmaceuticals Inc.

Chadds Ford, PA 19317

Manufactured by:

Pharmaceutical Associates, Inc.

Greenville, SC 29605

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