

HYCODAN - hydrocodone bitartrate and homatropine methylbromide tablet
HYCODAN - hydrocodone bitartrate and homatropine methylbromide solution

Endo Pharmaceuticals Inc.

ANTITUSSIVE

HYCODAN[®]

(Hydrocodone Bitartrate and Homatropine Methylbromide)

TABLETS AND ORAL SOLUTION

CIII

R_x only

DESCRIPTION

HYCODAN contains hydrocodone (dihydrocodeinone) bitartrate, a semisynthetic centrally-acting opioid antitussive. Homatropine methylbromide is included in a subtherapeutic amount to discourage deliberate overdose.

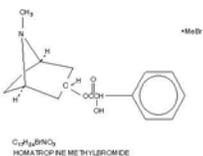
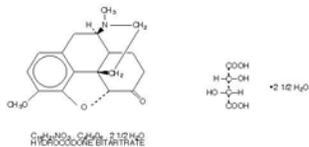
Each HYCODAN tablet or teaspoonful (5 mL) contains:

Hydrocodone Bitartrate, USP 5 mg

Homatropine Methylbromide, USP 1.5 mg

HYCODAN tablets also contain: calcium phosphate dibasic, colloidal silicon dioxide, lactose, magnesium stearate, starch and stearic acid.

HYCODAN oral solution also contains: caramel coloring, FD&C Red 40, liquid sugar, methylparaben, propylparaben, sorbitol solution and wild cherry imitation flavor. The hydrocodone component is 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5), a fine white crystal or crystalline powder, which is derived from the opium alkaloid, thebaine, has a molecular weight of (494.50), and may be represented by the following structural formula:



Homatropine methylbromide is 8-Azoniabicyclo [3.2.1]octane,3-[(hydroxyphenyl-acetyl)oxy]-8,8-dimethyl-,bromide, endo-; a white crystal or fine white crystalline powder, with a molecular weight of (370.29).

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, physical and physiological dependence.

Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 \pm 5.2 ng/mL. Maximum serum levels were achieved at 1.3 \pm 0.3 hours and the half-life was determined to be 3.8 \pm 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.

INDICATIONS AND USAGE

HYCODAN (hydrocodone bitartrate and homatropine methylbromide) is indicated for the symptomatic relief of cough in adults and children 6 years of age and older.

CONTRAINDICATIONS

HYCODAN should not be administered to patients who are hypersensitive to hydrocodone or homatropine methylbromide.

WARNINGS

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 HYCODAN 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

The use of HYCODAN is not recommended for use in children less than 6 years of age because of the risk of fatal respiratory depression (see **ADVERSE REACTIONS – Respiratory Depression**). HYCODAN produces dose-related respiratory depression by directly acting on brain stem respiratory centers. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated.

Head Injury and Increased Intracranial Pressure

The respiratory depression 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 HYCODAN or other opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Pediatric Use

In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of opioid cough suppressants in a dose-dependent manner. Caution should be exercised when administering HYCODAN to pediatric patients 6 years of age and older because of the potential for fatal respiratory depression. Overdose or concomitant administration of HYCODAN with other respiratory depressants may increase the risk of respiratory depression in pediatric patients. Benefit to risk ratio should be carefully considered especially in the pediatric population with respiratory embarrassment (e.g., croup) (see **PRECAUTIONS**).

PRECAUTIONS

General

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 physiological complications, and that appropriate therapy for the primary disease is provided.

Special Risk Patients

HYCODAN (hydrocodone bitartrate and homatropine methylbromide) should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal functions, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, asthma, and narrow-angle glaucoma.

Information for Patients

Hydrocodone may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using HYCODAN should be cautioned accordingly.

Patients should be advised to measure HYCODAN oral solution with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when a half a teaspoon is measured. A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose. Keep out of the reach of children.

Drug Interactions

Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with HYCODAN 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of HYCODAN in animals to evaluate the carcinogenic and mutagenic potential and the effect on fertility have not been conducted.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been conducted with HYCODAN. It is also not known whether HYCODAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HYCODAN 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.

Labor and Delivery

As with all opioids, administration of HYCODAN 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

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 HYCODAN, 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 HYCODAN in pediatric patients under six have not been established. The use of HYCODAN in children less than 6 years of age has been associated with cases of fatal respiratory depression (see **ADVERSE REACTIONS – Respiratory Depression**). HYCODAN should be used with caution in pediatric patients 6 years of age and older (see **WARNINGS – Pediatric Use**).

ADVERSE REACTIONS

Central Nervous System

Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes.

Gastrointestinal System

Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of HYCODAN may produce constipation.

Genitourinary System

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

Respiratory Depression

HYCODAN may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**). Use of HYCODAN in children less than 6 years of age has been associated with fatal respiratory depression. Overdose with HYCODAN in children 6 years of age and older, in adolescents, and in adults has been associated with fatal respiratory depression.

Postmarketing events seen in children under 6 years of age include accidental overdose, bronchopneumonia, coma, cyanosis, death, death neonatal, dyspnea, pulmonary edema, respiratory arrest, and respiratory depression.

Postmarketing events seen in patients older than 6 years of age include accidental overdose, cardio-respiratory arrest, death due to drug toxicity, non-accidental overdose, and overdose.

Dermatological

Skin rash, pruritus.

DRUG ABUSE AND DEPENDENCE

HYCODAN (hydrocodone bitartrate and homatropine methylbromide) is a Schedule III opioid. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of opioids; therefore, HYCODAN should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when HYCODAN is used for a short time for the treatment of cough. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy.

OVERDOSAGE

Signs and Symptoms

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 overdose, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of HYCODAN may, in addition, result in acute homatropine intoxication.

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.

DOSAGE AND ADMINISTRATION

It is important that HYCODAN oral solution is measured with an accurate measuring device (see **PRECAUTIONS – Information for Patients**). A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when a half a teaspoon is to be measured. It is strongly recommended that an accurate measuring device be used. A pharmacist can provide an appropriate measuring device and can provide instructions for measuring the correct dose.

Adults and Adolescents 12 years of Age and Older

One (1) tablet or 5 mL (1 teaspoonful) of the oral solution every 4 to 6 hours as needed; do not exceed six (6) tablets or 30 mL (6 teaspoonfuls) in 24 hours.

Children 6 to 11 Years of Age

One-half (1/2) tablet or 2.5 mL (1/2 teaspoonful) of the oral solution every 4 to 6 hours as needed; do not exceed three (3) tablets or 15 mL (3 teaspoonfuls) in 24 hours.

HOW SUPPLIED

HYCODAN is supplied as a white, biconvex tablet, one face bisected and debossed with “HYCODAN”, and the other face plain, available in:

Bottles of 100 NDC 63481-042-70

Bottles of 500 NDC 63481-042-85

Store tablets 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).

HYCODAN is also available as a clear red colored, wild cherry flavored oral solution in:

Bottles of one pint NDC 63481-234-16

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

Oral prescription where permitted by state law.

Manufactured for:

Endo Pharmaceuticals Inc.

Chadds Ford, Pennsylvania 19317

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/s/

Badrul Chowdhury
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