DISCLAIMER

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# Hydrocodone Bitartrate and Homatropine Methylbromide Syrup C II

**Rx only**

**ANTITUSSIVE**

**WARNING: 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, PRECAUTIONS - Drug Interactions). Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.**

## DESCRIPTION

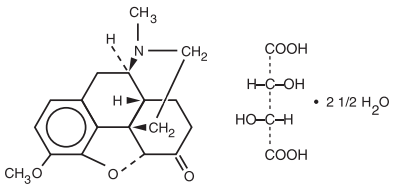
Hydrocodone Bitartrate and Homatropine Methylbromide Syrup contain hydrocodone (dihydrocodeinone) bitartrate, a semisynthetic centrally-acting opioid antitussive. Homatropine methylbromide is included in a subtherapeutic amount to discourage deliberate overdosage.

Each Hydrocodone Bitartrate and Homatropine Methylbromide Syrup teaspoonful (5 mL) contains:

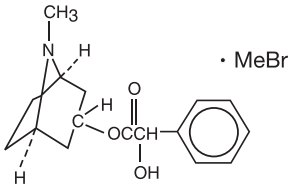
Hydrocodone Bitartrate, USP 5 mg
Homatropine Methylbromide, USP 1.5 mg

Hydrocodone Bitartrate and Homatropine Methylbromide Syrup also contains: Caramel color, cherry flavor, citric acid, FD&C Red #40, methylparaben, propylparaben, purified water, sorbitol solution and sucrose syrup. Citric acid and/or sodium citrate may be added to adjust pH.

The hydrocodone component is 4,5α-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:



$C_{18}H_{21}NO_3 \bullet C_4H_6O_6 \bullet 2\ 1/2H_2O$
HYDROCODONE BITARTRATE



$C_{17}H_{24}BrNO_3$
HOMATROPINE METHYLBROMIDE

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 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the 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.

## INDICATIONS AND USAGE

Hydrocodone bitartrate and homatropine methylbromide syrup is indicated for the symptomatic relief of cough in adults and children 6 years of age and older.

## CONTRAINDICATIONS

Hydrocodone bitartrate and homatropine methylbromide syrup should not be administered to patients who are hypersensitive to hydrocodone or homatropine methylbromide.

## WARNINGS

### Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including hydrocodone bitartrate and homatropine methylbromide syrup, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedations, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol (see **PRECAUTIONS - Drug Interactions**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if hydrocodone bitartrate and homatropine methylbromide syrup is used with benzodiazepines, alcohol, or other CNS depressants (see **PRECAUTIONS - Information for Patients**).

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 hydrocodone bitartrate and homatropine methylbromide 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

The use of hydrocodone bitartrate and homatropine methylbromide syrup 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**). Hydrocodone bitartrate and homatropine methylbromide syrup 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 hydrocodone bitartrate and homatropine methylbromide syrup 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 hydrocodone bitartrate and homatropine methylbromide syrup to pediatric patients 6 years of age and older because of the potential for fatal respiratory depression. Overdose or concomitant administration of hydrocodone bitartrate and homatropine methylbromide syrup 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

Hydrocodone bitartrate and homatropine methylbromide syrup 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

Inform patients and caregivers that potentially fatal additive effects may occur if hydrocodone bitartrate and homatropine methylbromide syrup is used with benzodiazepines or other CNS depressants, including alcohol. Because of this risk, patients should avoid concomitant use of hydrocodone bitartrate and homatropine methylbromide syrup with benzodiazepines or other CNS depressants, including alcohol (see **WARNINGS, PRECAUTIONS - Drug Interactions**).

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 hydrocodone bitartrate and homatropine methylbromide syrup should be cautioned accordingly.

Patients should be advised to measure hydrocodone bitartrate and homatropine methylbromide syrup 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

The use of benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and homatropine methylbromide syrup may cause an additive CNS depressant effect, profound sedation, respiratory depression, coma, and death and should be avoided (see **WARNINGS**).

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 hydrocodone bitartrate and homatropine methylbromide syrup 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 hydrocodone bitartrate and homatropine methylbromide syrup. It is also not known whether HYCODAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hydrocodone bitartrate and homatropine methylbromide 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.

**Labor and Delivery**
As with all opioids, administration of hydrocodone bitartrate and homatropine methylbromide syrup 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 hydrocodone bitartrate and homatropine methylbromide syrup, 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 hydrocodone bitartrate and homatropine methylbromide syrup in pediatric patients under six have not been established. The use of hydrocodone bitartrate and homatropine methylbromide syrup 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**
To report SUSPECTED ADVERSE REACTIONS, contact Hi-Tech Pharmacal Co., Inc. at 1-800-262-9010 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**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 hydrocodone bitartrate and homatropine methylbromide syrup may produce constipation.

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

**Respiratory Depression**
Hydrocodone bitartrate and homatropine methylbromide syrup may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**). Use of hydrocodone bitartrate and homatropine methylbromide syrup in children less than 6 years of age has been associated with fatal respiratory depression. Overdose with hydrocodone bitartrate and homatropine methylbromide syrup 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, cardiorespiratory arrest, death due to drug toxicity, non-accidental overdose, and overdose.

**Dermatological**
Skin rash, pruritus.

**DRUG ABUSE AND DEPENDENCE**
Hydrocodone bitartrate and homatropine methylbromide syrup is Schedule II opioids. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of opioids; therefore, hydrocodone bitartrate and homatropine methylbromide syrup should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and homatropine methylbromide syrup 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 overdosage 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. The ingestion of very large amounts of hydrocodone bitartrate and homatropine methylbromide syrup 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 hydrocodone bitartrate and homatropine methylbromide syrup 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) teaspoonful (5 mL) of the syrup every 4 to 6 hours as needed; do not exceed 30 mL six (6 teaspoonfuls) in 24 hours.

**Children 6 to 11 Years of Age**
One-half (1/2) teaspoonful (2.5 mL) of the syrup every 4 to 6 hours as needed; do not exceed 15 mL (3 teaspoonfuls) in 24 hours.

**HOW SUPPLIED**
Hydrocodone Bitartrate and Homatropine Methylbromide Syrup is available as a clear red colored, cherry flavored syrup in:

Bottles of 16 fl. oz. (one pint)

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container, as defined in the USP.

Oral prescription where permitted by state law.

Manufactured By:
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