

# COMPLETE PRESCRIBING INFORMATION

## <sup>N</sup> HYCODAN\* TABLETS

(hydrocodone bitartrate, USP)  
5 mg

## <sup>N</sup> HYCODAN\* SYRUP

(hydrocodone bitartrate)  
5 mg/5 ml

**Antitussive**

Bristol-Myers Squibb Canada  
Montreal, Canada

Date of Preparation:  
September 13, 1983

Date of Revision:  
November 5, 2001  
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# PRODUCT MONOGRAPH

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(hydrocodone bitartrate, USP)  
5 mg

**<sup>N</sup> HYCODAN\* SYRUP**  
(hydrocodone bitartrate)  
5 mg/5 ml

## THERAPEUTIC CLASSIFICATION

Antitussive

## ACTION AND CLINICAL PHARMACOLOGY

Clinical trials have proven hydrocodone bitartrate to be an effective antitussive agent which is pharmacologically two to eight times as potent as codeine. At equieffective doses, its sedative action is greater than that of codeine. The precise mechanisms of action of hydrocodone and other opiates are 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 therapeutic doses of hydrocodone on the cardiovascular system are insignificant. The constipating effects of hydrocodone are much weaker than those of morphine and no stronger than those 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 serum 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- $\alpha$ - and 6- $\beta$ -hydroxymetabolites.

## INDICATIONS

The control of exhausting, non-productive cough.

## CONTRAINDICATIONS

HYCODAN\* TABLETS and SYRUP should not be used in patients with hypersensitivity to any component of the drug. Patients known to be hypersensitive to other opioids may exhibit cross sensitivity to hydrocodone. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure, and whenever ventilatory function is depressed.

## WARNINGS

### **Drug abuse and dependence**

Hydrocodone can produce drug dependence and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of hydrocodone, and it should be prescribed and administered with the same

degree of caution appropriate to the use of other narcotic drugs (see DRUG ABUSE AND DEPENDENCE).

### **Respiratory depression**

Hydrocodone 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 naloxone hydrochloride (NARCAN\*) and other supportive measures when indicated.

### **Usage in ambulatory patients:**

Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients using HYCODAN\* TABLETS or SYRUP should be cautioned accordingly.

### **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 pre-existing elevated intracranial pressure. Furthermore, narcotics may produce adverse reactions which can obscure the clinical course of patients with head injuries.

### **Acute abdominal conditions**

The administration of hydrocodone or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

### **Interaction with other central nervous system depressants**

Patients receiving other narcotic analgesics, general anesthetics, phenothiazines or other tranquilizers, tricyclic antidepressants, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with HYCODAN\* TABLETS or SYRUP may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

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

In young children the respiratory centre is especially susceptible to the depressant action of narcotic cough suppressants. Benefit to risk ratio should be carefully considered, especially in children with respiratory embarrassment, e.g., croup. Estimation of dosage relative to the child's age and weight is of great importance.

As hydrocodone may inhibit peristalsis, patients with chronic constipation should be given the drug only after weighing the potential therapeutic benefit against the hazards involved. In patients with asthma or pulmonary emphysema, indiscriminate use may precipitate respiratory insufficiency resulting from increased viscosity of bronchial secretions and suppression of the cough reflex.

Use with caution in sedated or debilitated patients, in patients who have undergone thoracotomies or laparotomies, since suppression of the cough reflex may lead to retention of secretions postoperatively in these patients.

### **Drug interactions**

The central nervous system depressant effect of HYCODAN\* TABLETS and SYRUP may be additive with that of other central nervous system depressants. See WARNINGS.

### **Carcinogenesis, mutagenesis, impairment of fertility**

Carcinogenicity, mutagenicity and reproduction studies have not been conducted with HYCODAN\* TABLETS and SYRUP.

### **Usage in pregnancy**

Animal reproduction studies have not been conducted with HYCODAN\* TABLETS and SYRUP. It is also not known whether HYCODAN\* TABLETS and SYRUP can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Since hydrocodone crosses the placental barrier, HYCODAN\* TABLETS and 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 opioids use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7 to 1.0 mg/kg q6h, phenobarbital 2 mg/kg q6h, and paregoric 2 to 4 drops/kg q4h, 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 HYCODAN\* TABLETS and 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.

## **DRUG INTERACTIONS**

The central nervous system depressant effect of hydrocodone may be additive with that of other central nervous system depressants. See WARNINGS.

## **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. Constipation may also occur.

**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.

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics, therefore HYCODAN\* TABLETS and 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 narcotic 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.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE****Signs and Symptoms**

Serious overdosage with hydrocodone may be 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 re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone (NARCAN\*) is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. An appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. The instructions contained in the package insert should be carefully observed. 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 Dosage**

One HYCODAN\* TABLET or 5 ml (one teaspoonful) of HYCODAN\* SYRUP not less than 4 hours apart, after meals and at bedtime with food or a glass of milk, not to exceed six tablets or 30 ml (six teaspoonfuls) of syrup in a 24-hour period. Maximum single dose three tablets or 15 ml (three teaspoonfuls) of syrup.

#### **Usual Children's Dosage**

Over 12 yrs: One HYCODAN\* TABLET or 5 ml (one teaspoonful) of HYCODAN\* SYRUP not less than 4 hours apart, after meals and at bedtime with food or a glass of milk, not to exceed 30 ml (six teaspoonfuls) in a 24-hour period. Maximum single dose two tablets or 10 ml (two teaspoonfuls) of syrup.

Age 2 to 12 yrs: One half of a HYCODAN\* TABLET or 2.5 ml (1/2 teaspoonful) of HYCODAN\* SYRUP not less than 4 hours apart, after meals and at bedtime with food or a glass of milk, not to exceed a total of three tablets or 15 ml (three teaspoonfuls) of syrup in a 24-hour period. Maximum single dose one tablet or 5 ml (1 teaspoonful) of syrup.

Age less than 2 yrs: One quarter of a HYCODAN\* TABLET or 1.25 ml (1/4 teaspoonful) of HYCODAN\* SYRUP not less than 4 hours apart, after meals and at bedtime with food or a glass of milk, not to exceed a total of 1 1/2 tablets or 7.5 ml (1 1/2 teaspoonfuls) of syrup in a 24-hour period. Maximum single dose 1/4 tablet or 1.25 ml (1/4 teaspoonful) of syrup.

### **PHARMACEUTICAL INFORMATION**

Each tablet and each 5 ml (teaspoonful) of syrup contain: hydrocodone bitartrate 5 mg. The syrup also contains sucrose.

Hydrocodone is 7,8-dihydrocodeinone, a derivative of codeine.

Empirical Formula:  $C_{18}H_{21}NO_3$

Molecular Weight: 299.36

### **DOSAGE FORMS**

#### **HYCODAN\* TABLETS**

Each white, biconvex and bisected tablet contains: hydrocodone bitartrate 5 mg. Nonmedicinal ingredients: cornstarch, lactose, pregelatinized tapioca starch, stearic acid, talc and zinc stearate. Sodium- and tartrazine-free. Supplied in bottles of 100 tablets.

#### **HYCODAN\* SYRUP**

Each 5 mL of red, wild cherry-flavored syrup contains: hydrocodone bitartrate 5 mg. Nonmedicinal ingredients: artificial cherry flavour, caramel syrup, FD&C RED No. 2, hydrochloric acid, methylparaben, propylparaben, purified water, sorbitol solution 70% and sucrose. Alcohol-, lactose-, sodium-, sulfite- and tartrazine-free. Supplied in bottles of 500 ml.

#### **Storage**

Patients should be instructed to store HYCODAN\* TABLETS and SYRUP, as for any medication, well out of the reach of children. Keep tightly closed. Store at 15° to 30 °C. Dispense HYCODAN\* SYRUP in a tight, light-resistant container.