

# COMPLETE PRESCRIBING INFORMATION

## <sup>N</sup> HYCOMINE\*

(hydrocodone bitartrate 5mg/5ml, pyrilamine maleate 12.5mg/5ml  
phenylephrine HCl 10mg/5ml, ammonium chloride 60mg/5ml)

Syrup

**Antitussive / Antihistaminic / Decongestant**

Bristol-Myers Squibb Canada  
Montreal, Canada

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#### Syrup

#### THERAPEUTIC CLASSIFICATION

Antitussive / Antihistaminic / Decongestant

#### 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 equi-effective 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.

Pyrilamine maleate is a competitive H<sub>1</sub>-receptor histamine blocking drug, thereby counteracting the effects of histamine release associated with allergic manifestations of upper respiratory tract inflammatory disorders. H<sub>1</sub>-blocking drugs inhibit the actions of histamine on smooth muscle, capillary permeability, and can both stimulate and depress the central nervous system.

Phenylephrine hydrochloride effects its vasoconstrictor activity by releasing noradrenaline from sympathetic nerve endings, and from direct stimulation of  $\alpha$ -adreno-receptors in blood vessels.

Ammonium chloride exerts an expectorant effect by virtue of a local action on the gastric mucosa.

#### INDICATIONS

To control cough, and to provide symptomatic relief of congestion in the upper respiratory tract due to the common cold, nasopharyngitis, tracheitis, and bronchitis, which do not respond to products of lesser potency.

#### CONTRAINDICATIONS

HYCOMINE<sup>®</sup> SYRUP should not be used in patients with hypersensitivity to any component of the drug. Patients known to be hypersensitive to other opioids, antihistamines or sympathomimetic amines may exhibit cross sensitivity to hydrocodone, pyrilamine or phenylephrine. Should not be used in patients using monoamine oxidase inhibitors.

Phenylephrine is contraindicated in patients with heart disease, hypertension, diabetes or hyperthyroidism. 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 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 HYCOMINE<sup>®</sup> 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 HYCOMINE<sup>®</sup> SYRUP may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

### **Phenylephrine**

Hypersensitive crises can occur with concurrent use of phenylephrine and monoamine oxidase (MAO) inhibitors, indomethacin or with beta-blockers and methyl dopa.

If a hypertensive crisis occurs these drugs should be discontinued immediately and therapy to

lower blood pressure should be instituted immediately. Fever should be managed by means of external cooling.

### **Pyrilamine**

Antihistamines may produce drowsiness or excitation, particularly in children and elderly patients.

### **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.

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 the 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.

Use with caution in glaucoma, prostatic hypertrophy, urinary retention, and in the aged.

### **Drug interactions**

The central nervous system depressant effect of HYCOMINE<sup>+</sup> 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 HYCOMINE<sup>+</sup> SYRUP.

### **Usage in pregnancy**

Animal reproduction studies have not been conducted with HYCOMINE<sup>+</sup> SYRUP. It is also not known whether HYCOMINE<sup>+</sup> SYRUP can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Since hydrocodone crosses the placental barrier, HYCOMINE<sup>+</sup> 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 HYCOMINE<sup>+</sup> 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 HYCOMINE<sup>+</sup> SYRUP 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, tachycardia 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 HYCOMINE<sup>+</sup> 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. Manifestation 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**

The signs and symptoms of overdosage of the individual components of HYCOMINE \* SYRUP may be modified in varying degrees by the presence of other active ingredients.

#### **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 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**

5 ml (one teaspoonful) after meals and at bedtime with food or a glass of milk, at intervals of not

less than four hours, not to exceed 30 ml (six teaspoonfuls) in a 24-hour period. Maximum single dose 15 ml (three teaspoonfuls).

### **PHARMACEUTICAL INFORMATION**

Each 5 ml (teaspoonful) contains: hydrocodone bitartrate 5 mg, pyrilamine maleate 12.5 mg, phenylephrine HCl 10 mg, ammonium chloride 60 mg. Nonmedicinal ingredients: casiline orange, cherry flavour, hydrochloric acid, methylparaben, propylparaben, purified water, sorbitol solution and sucrose. Alcohol-, lactose-, sodium-, sulfite- and tartrazine- free.

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

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

Molecular Weight: 299.36

#### **Pyrilamine maleate**

Empirical Formula:  $C_{17}H_{23}N_3O \cdot C_4H_4O_4$

Molecular Weight: 401.46

#### **Phenylephrine hydrochloride**

Empirical Formula:  $C_9H_{13}NO_2HCL$

Molecular Weight: 203.67

### **DOSAGE FORMS**

HYCOMINE<sup>®</sup> is supplied as an orange, cherry-flavoured with a sucrose base, in bottles of 500 ml.

#### **Storage**

Patients should be instructed to store HYCOMINE<sup>®</sup> SYRUP, as for any medication, well out of the reach of children. Keep tightly closed. Store at 15° to 30°C. Dispense in a tight, light-resistant container.