PRESCRIBING INFORMATION

Ⓝ CALMYLIN

Codeine phosphate 3.33 mg/5 mL –Diphenhydramine hydrochloride 12.5 mg/5 mL

Ammonium chloride 125 mg/5 mL

Liquid

Antitussive - Antihistamine – Expectorant

Ⓝ CALMYLIN PSE WITH CODEINE

Codeine phosphate 3.3 mg/5mL –Pseudoephedrine HCl 30 mg /5mL –

Guaifenesin 100 mg/5mL

Liquid

Antitussive – Decongestant – Expectorant

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PRESCRIBING INFORMATION

Ⓝ CALMYLIN

Codeine phosphate - Diphenhydramine HCl - Ammonium chloride

Antitussive – Antihistamine – Expectorant

Ⓝ CALMYLIN PSE WITH CODEINE

Codeine phosphate - Pseudoephedrine HCl - Guaifenesin

Antitussive – Decongestant - Expectorant

INDICATIONS AND CLINICAL USE

Calmylin is indicated for suppression of dry, hacking cough, symptomatic treatment of various immediate allergic reactions and to loosen mucus/phlegm in cough due to colds.

Calmylin PSE with Codeine is indicated for suppression of dry, hacking cough, for relief of nasal congestion and to loosen mucus/phlegm in cough due to colds.

Pediatrics

Regardless of clinical setting, the use of codeine, including **CALMYLIN and CALMYLIN PSE with Codeine** is not recommended in patients below the age of 12 years due to increased safety concerns (see **WARNINGS AND PRECAUTIONS, Pediatrics**).

CLINICAL PHARMACOLOGY:

Ammonium Chloride:

Ammonium Chloride is used as an expectorant in productive cough. It increases the volume of secretions in the respiratory tract thus facilitating removal by ciliary action and coughing.

Diphenhydramine Hydrochloride:

Diphenhydramine is a first generation H1 receptor antagonist of the ethanolamine class. Most antihistamines cross the blood-brain barrier and produce sedation due to inhibition of histamine N-methyltransferase and blockage of central histaminergic receptors. Antagonism of other central nervous system receptor sites, such as those for serotonin, acetylcholine, and alpha- adrenergic stimulation, may also be involved.

Diphenhydramine hydrochloride is well-absorbed following oral administration, but undergoes first-pass metabolism in the liver and only about 40-60% of an oral dose reaches systemic circulation as unchanged diphenhydramine.

Following oral administration of a single dose of diphenhydramine, the drug appears in plasma within 15 minutes and peak plasma concentrations are attained within 1-4 hours.

Following oral administration of diphenhydramine hydrochloride dosages of 25 mg every 4 hours or 50 mg every 6 hours, peak steady-state plasma concentrations of the drug were 55 or 85 ng/mL, respectively, and minimum peak steady-state plasma concentrations were 27.5 or 30 ng/mL, respectively.

Guaifenesin:

Guaifenesin is thought to act by irritating the gastric mucosa and subsequently stimulating respiratory tract secretions. This increase in fluid increases the volume and decreases the viscosity of bronchial secretions. By reducing the viscosity and adhesiveness of secretions, guaifenesin increases the efficacy of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway. The increased flow of less viscous secretions promotes ciliary action and changes a dry, unproductive cough to one that is more productive and less frequent.

Guaifenesin is well absorbed from the gastrointestinal tract and the plasma half-life is 1 hour. Guiafenesin is rapidly hydrolyzed (60% within seven hours) and then excreted in the urine, with beta-(2-methoxyphenoxy)-lactic acid as its major urinary metabolite. No unchanged drug was detected in the urine following administration.

Pseudoephedrine HCl:

Pseudoephedrine HCl is a decongestant and acts on alpha-adrenergic receptors in the mucosa of the respiratory tract, producing vasoconstriction. The medication shrinks swollen nasal mucous membranes; reduces tissue hyperemia, edema, and nasal congestion; and increases nasal airway patency. Also, drainage of sinus secretions may be increased and obstructed eustachian ostia may be opened.

Pseudoephedrine may cause mild CNS stimulation, especially in patients who are sensitive to the effects of sympathomimetics drugs.

Pseudoephedrine is absorbed from the gastrointestinal tract, is incompletely metabolized in the liver to norpseudoephedrine, the primary active metabolite of the parent and the drug and the metabolite are excreted in the urine. Approximately 50 to 75% of a dose is excreted as unchanged drug. Nasal decongestion occurs within 30 minutes and persists for 4-6 hours.

Codeine phosphate:
Codeine phosphate is an opioid analgesic and antitussive. Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral potency of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10% of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

CONTRAINDICATIONS

CALMYLIN (Codeine phosphate – Diphenhydramine HCl – Ammonium chloride) should not be administered to patients who have previously exhibited hypersensitivity to any of the components or have pre-existing respiratory depression.

CALMYLIN PSE with Codeine (Codeine phosphate – Pseudoephedrine HCl - Guaifenesin) should not be administered to patients who have previously exhibited hypersensitivity to any of the components, have pre-existing respiratory depression, and in patients receiving or having received monoamine oxidase (MAO) inhibitor drugs in the preceding 3 weeks.

WARNINGS AND PRECAUTIONS

Caution: This preparation contains codeine and should not be adminis tered to children except on the advice of a physician.

Keep this product and all medicine out of the reach of children.

Do not exceed recommended dosage.
This package contains enough drug to seriously harm a child.

Stop use and consult a doctor if symptoms or cough worsen or persist for more than 7 days or if high fever, rash or persistent headache is present, as these may be signs of a serious condition.

Codeine:

Patients should be counselled to consult a physician before use if they are taking other medications that can make them sleepy or less alert, for example: narcotic analgesics or sedating antihistamines, or they are currently taking anti-depressants, other prescription drugs or natural health products or 3 or more alcoholic beverages per day, or if they have recently had surgery under general anaesthesia.

Patients should be counselled to consult a physician before use if they have difficulty breathing, have asthma or other chronic lung disease.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine produces dose-related respiratory depression. Caution should be exercised when drug product with codeine is used postoperatively, in patients with pulmonary disease or shortness of breath or whenever ventilatory function is depressed.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Use with caution in patients with seizures as the seizures may be exacerbated or induced by opioids.

Codeine is habit forming and potentially abusable. Consequently, the extended use of this product is not recommended.

Guaifenesin: Not recommended for patients with asthma unless directed by a physician.

Diphenhydramine: Diphenhydramine has an atropine-like action which should be considered when prescribing this product to patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.

Pseudoephedrine: Should be used with caution in diabetics, high blood pressure, hypertensive patients and patients with glaucoma, coronary artery disease, hyperthyroidism and urinary retention due to prostate enlargement.

Prolonged use may have a constipating effect by inhibition of peristalsis; patients with chronic constipation should be given **CALMYLIN or CALMYLIN PSE WITH CODEINE** only after weighing the potential therapeutic benefit against the hazards involved.

General

CALMYLIN (Codeine phosphate – Diphenhydramine HCl – Ammonium chloride) and **CALMYLIN PSE with Codeine** (Codeine phosphate – Pseudoephedrine HCl - Guaifenesin) should not be administered to patients who have previously exhibited hypersensitivity to any of the components or have pre-existing respiratory depression.

If the patient has high blood pressure, coronary artery disease, heart or thyroid disease, diabetes, glaucoma, asthma, chronic lung disease, shortness of breath,

persistent/chronic cough or difficulty in urination due to an enlargement of the prostate gland, or if you are elderly, pregnant or breast-feeding or taking a drug for depression including monoamine oxidase (MAO) inhibitor drugs, consult a physician before using this product.

Ultra-Rapid Metabolizers of Codeine

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about these risks and the signs of morphine overdose (see **WARNINGS AND PRECAUTIONS, Lactation**).

Respiratory

Codeine, including CALMYLIN and CALMYLIN PSE with Codeine, is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

With diphenhydramine therapy, thickening of bronchial secretions, tightening of chest, wheezing and nasal stuffiness have been reported.

Skin

Pseudoephedrine may induce non-pigmenting, fixed-type skin eruptions, which are typically indurated, erythematous, pruritic, tender, and oedematous. The reaction tends

to occur within 24 hours after administration of pseudoephedrine and to resolve 2 to 3 days after discontinuation.

Lactation

Codeine:

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, **some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants**.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding (see **WARNINGS AND PRECAUTIONS, Ultra-Rapid Metabolizers of Codeine**).

Diphenhydramine:

Evidence suggests that diphenhydramine may alter milk production or composition. If an alternative drug is not prescribed, infants' adequate intake of milk should be monitored. It is not known whether diphenhydramine is excreted into milk.

Occupational Hazards

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks. Patients using this drug should be cautioned about driving a car or operating potentially hazardous machinery if they become drowsy or show impaired mental or physical abilities while taking this medication.

The patient should understand the single-dose and 24-hour dose limits, and the time interval between doses. Like other narcotic-containing medications, these drugs are subject to the Controlled Drugs and Substances Act.

Diphenhydramine delivers a sedative effect. Alcohol and other CNS depressants may increase this effect. Caution should be used when driving a motor vehicle or operating machinery (See **Drug Interactions**).

Drug Interactions

This drug may enhance the effects of other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Do not use with a monoamine oxidase (MAO) inhibitor or for 2 weeks after stopping the MAO inhibitor drug.

Since the depressant effects of diphenhydramine, pseudoephedrine and codeine are additive to those of other drugs affecting the CNS, patients should be cautioned against drinking alcoholic beverages or taking hypnotics, sedatives, psychotherapeutic agents or other antihistamine and CNS depressant drugs (such as MAO inhibitors, phenothiazines or tricyclic antidepressants).

Drug/Laboratory Test Interactions

Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to whether codeine have a potential for carcinogenesis or mutagenesis.

Codeine has been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Special Populations

Pregnant Women:

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study, a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no adequate and well-controlled studies in pregnant women.

Dependence and withdrawal signs have been reported in newborns whose mothers took opiates regularly during pregnancy. These signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. Signs usually appear during the first few days of life.

Diphenhydramine: No controlled studies have been done in women or animals.

Diphenhydramine may cause an increased level of uterine activity and may lead to premature labour. Caution should be exercised with its use during the latter part of pregnancy.

Labour and Delivery:

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labour if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labour, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see **OVERDOSAGE**). The effects of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Pediatrics

CALMYLIN and CALMYLIN PSE with Codeine should not be administered to children less than 12 years of age.

Geriatrics (> 65 years of age):

Patients older than 65 years and frail or debilitated patients may be more susceptible to the adverse effects of diphenhydramine and codeine, especially respiratory depression. Use with caution; the initial dose should be reduced and the effects monitored.

The administration of codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Codeine should not be used in patients with diarrhea associated with pseudomembranous colitis. Use with caution in patients with acute ulcerative colitis or other severe inflammatory bowel disease due to the risk of toxic megacolon.

Caution should be exercised and dosage may need to be reduced when administered with other drugs that depress the CNS (including alcohol), with MAO inhibitors, phenothiazines or tricyclic antidepressants.

Consult your doctor if you feel sedated or drowsy, confused, have shallow breathing or have severe constipation. Do not administer to patients with glaucoma or prostate enlargement.

Drug Abuse and Dependence

Codeine 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 CALMYLIN and CALMYLIN PSE with Codeine. These drugs should be administered with the same degree of caution appropriate to the use of other oral narcotic- containing medications.

ADVERSE REACTIONS

Adverse reactions due to codeine phosphate may include drowsiness, nausea, vomiting and constipation. Infrequent adverse effects include palpitation, dry mouth, skin rash, pruritus and, rarely, hyperhidrosis and agitation have been reported. Respiratory depression is seen in higher dosage, and there is a potential for tolerance, psychological dependence or physical dependence to occur.

Diphenhydramine delivers a sedative effect. Alcohol and other CNS depressants may increase this effect.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In Case of Accidental Overdose: Call a Poison Control Centre or doctor immediately, even if you do not notice any signs or symptoms such as increased sweating, nausea, vomiting, stomach pain or loss of appetite.

Symptoms:
May result in euphoria, dysphoria, visual disturbance, hypotension and coma or death from respiratory depression.

Treatment:

Codeine:
Typical Toxidrome: Narcotic/Opiate
Specific Antidote: Naloxone HCl.
General Management: Stabilize the patient (A, B, C's), undertake appropriate gastrointestinal tract decontamination procedures, initiate supportive care, administer antidote as needed (see manufacturer's product monograph), consult with a Regional Poison Control Centre regarding ongoing management, and arrange for appropriate follow-up care.

DOSAGE AND ADMINISTRATION

Dosing Considerations

CALMYLIN and CALMYLIN PSE with Codeine should not be used in children less than 12 years old.

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of the cough is identified, that modification of the cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

Adults 12 years and over

DOSAGE: Ⓝ **CALMYLIN:** 2 teaspoonful (10 mL) every three to four hours, maximum of 4 doses per day or as prescribed by a physician.

Ⓝ **CALMYLIN PSE WITH CODEINE:** 2 teaspoonful (10 mL) every 4 hours, maximum of 4 doses per day or as prescribed by a physician.

Do not co-administer with other drugs containing same medicinal ingredients.

AVAILABILITY OF DOSAGE FORMS

SUPPLIED: Ⓝ **CALMYLIN:**
Each 5 mL (1 teaspoonful) contains: Codeine phosphate 3.33 mg, diphenhydramine hydrochloride 12.5 mg and ammonium chloride 125 mg.
Non-medicinal ingredients in alphabetical order: FD & C yellow # 6, alcohol, amaranth, glycerin, menthol, purified water, raspberry flavour, simethicone, sorbitol and sucrose.
Energy: 17.28 kcal/5 mL. Gluten- and tartrazine- free. Bottles of 100 mL, 250 mL and 350 mL.

Ⓝ **CALMYLIN PSE WITH CODEINE:**
Each 5 mL (1 teaspoonful) contains: Codeine phosphate 3.33 mg, pseudoephedrine hydrochloride 30 mg and guaifenesin 100 mg.
Non-medicinal ingredients in alphabetical order: FD & C yellow # 6, alcohol, amaranth, citric acid, glycerin, maltitol, menthol, methylparaben, propyleneglycol, propylparaben, purified water, raspberry flavour, sodium chloride, sodium citrate, sodium cyclamate and sorbitol.
Energy: 10.42 kcal/5 mL. Gluten-, tartrazine-, and sucrose -free. Bottles of 100 mL, 250 mL and 350 mL.

STORAGE AND STABILITY
Store between 15-30°C.

REFERENCES

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6. Health and Welfare Canada. Regulatory Proposals Regarding Antihistamines, Nasal Decongestants and Anticholinergics In Nonprescription Cough and Cold Remedies. Health Protection Branch Information Letter No.784, 1990.

MORE INFORMATION

Additional copies of this documentis available to health professionals by contacting the sponsor, Teva Canada Limited, at:

1-800-268-4127 ext. 1255005 (**English**)
1-877-777-9117 (**French**)
or druginfo@tevacanada.com

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