

PRESCRIBING INFORMATION

Ⓝ CALMYLIN ACE

Guaifenesin, Codeine Phosphate and Pheniramine Maleate Syrup

Guaifenesin 100 mg/5 mL - Codeine Phosphate 10 mg/5 mL –
Pheniramine Maleate 7.5 mg/5 mL

Expectorant/ Cough Suppressant/ Antihistamine

**Teva Canada Limited.
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Canada M1B 2K9
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DATE OF REVISION:
July 10, 2014

Control #: 175077

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SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage form/ Strength | Non-medicinal Ingredients |
|--------------------------------|--|---|
| Oral | Syrup, each 5 mL of which contains: guaifenesin 100 mg, codeine phosphate 10 mg and pheniramine maleate 7.5 mg | alcohol, artificial coloring and flavoring, caramel, citric acid, FD&C yellow #6, glycerine, menthol, propylene glycol, purified water, sodium benzoate, sodium citrate dehydrate, sodium cyclamate and sucrose. Alcohol: 4.1 % v/v. Sucrose: 45 %. |

INDICATIONS AND CLINICAL USE

Ⓝ CALMYLIN ACE is indicated:

To facilitate expectoration and control cough associated with inflamed mucosa temporarily.

Pediatrics

Regardless of clinical setting, the use of codeine, including Ⓝ CALMYLIN ACE, is not recommended in patients below the age of 12 years due to increased safety concerns (see Warnings and Precautions/ Use in Children)

CONTRAINDICATIONS

Ⓝ CALMYLIN ACE is contraindicated in:

- Patients with allergy or hypersensitivity to codeine, guaifenesin or pheniramine, any of the listed ingredients, or pre-existing respiratory depression.
- Do not use with a monoamine oxidase inhibitor (MAOI) or for 2 weeks after stopping the MAOI drug.
- Patients allergic to codeine or other opioids, have suffered head injury, are at risk of blocked intestines or suffer from seizures.

WARNINGS AND PRECAUTIONS

General

Keep out of reach and sight 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.

Do not use without consulting your physician if you have a persistent or chronic cough (as occurs with smoking), breathing problems, chronic lung disease (e.g. chronic bronchitis, asthma or emphysema), glaucoma, high blood pressure, heart or thyroid disease, diabetes, prostate enlargement and bladder neck obstruction, difficulty urinating due to an enlarged prostate, if you are pregnant, nursing, or are under a physician's care.

Codeine may cause harm to a breast fed baby. **Contact your doctor immediately** if you are breastfeeding and your baby is having difficulty breathing or feeding, or is very sleepy or limp. Sedatives and tranquilizers may increase drowsiness.

Product may cause drowsiness or excitability. Avoid alcohol, driving a motor vehicle or operating machinery.

Tolerance, psychological dependence and physical dependence may develop in patients receiving codeine phosphate over a prolonged period.

Use with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve and patients with pre-existing respiratory depression, hypoxia or hypercapnia. Usual therapeutic doses may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. In patients with asthma or pulmonary emphysema, codeine may, due to its drying action on the respiratory mucosa, increase viscosity of bronchial secretions and suppress 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.


The respiratory depressant effects of codeine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury or intracranial lesions or pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of a patient with head injuries. In such patients, codeine must be used with extreme caution and only if its use is deemed essential.

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

Use with caution in patients with cardiac arrhythmias due to the cholinergic effects of the drug.

Codeine should be given with caution and the initial dose should be reduced in certain patients such as the debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Respiratory

Codeine, including  CALMYLIN ACE 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.

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 and shallow breathing.

Occupational Hazards:

Warn patients against driving or operating machinery if they become drowsy or show impaired mental and/or physical abilities while taking codeine.

Drug Interactions

Do not use if have taken or are taking; medication in the last 14 days for high blood pressure or depression, including other antitussives, antihistamines, other products that contain codeine, decongestants, expectorants, tranquilizers, sedating drugs or if you consume 3 or more alcoholic beverages a day.

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

Use in Pregnancy

Since codeine phosphate crosses the placental barrier, its use in pregnancy is not recommended.

Use in Lactation

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 (see Ultra-Rapid Metabolizers of Codeine). These women achieve higher-than expected levels of morphine in breastmilk and potentially dangerously high serum morphine levels in their breastfed infants. 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. 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, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Americans, 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 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. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding.

Codeine is excreted in small amounts which are probably insignificant with usual analgesic or antitussive doses.

Use in Elderly

Elderly patients may be more susceptible to the adverse effects of 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.

Use in Children:

- Ⓝ CALMYLIN ACE may cause drowsiness or excitability, especially in children.
- Ⓝ CALMYLIN ACE is not recommended for children under 12 years of age.

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.

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Take 10 mL (2 tsp) every 4 to 6 hours as follows or as directed by a doctor. Do not exceed 6 doses (12 tsp.) in a 24-hour period.

Children under 12 years

Ⓝ CALMYLIN ACE is not recommended for children under 12 years of age.

Codeine, including Ⓝ CALMYLIN ACE, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

OVERDOSAGE

Symptoms:

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

Treatment:

Symptomatic and supportive therapy. Maintain ventilation and administer oxygen as needed. The narcotic antagonist naloxone should be administered. If the patient is conscious and has not lost the gag reflex, empty the stomach by inducing emesis with ipecac syrup. If the patient is extremely drowsy, unconscious, convulsing or has no gag reflex, perform gastric lavage. Follow with activated charcoal (50 to 100 g in adults) and a cathartic.

In case of accidental overdose, contact a physician or poison control centre immediately, even if there are no symptoms.

| |
|---|
| For management of a suspected drug overdose, contact your regional Poison Control Centre immediately. |
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STORAGE AND STABILITY

Store between 15-30°C, protect from light.

Others:

Keep in a safe place out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 5 mL of cherry-flavored, clear, orange syrupy liquid with a menthol odor contains:
guaifenesin 100 mg, pheniramine maleate 7.5 mg and codeine phosphate 10 mg.

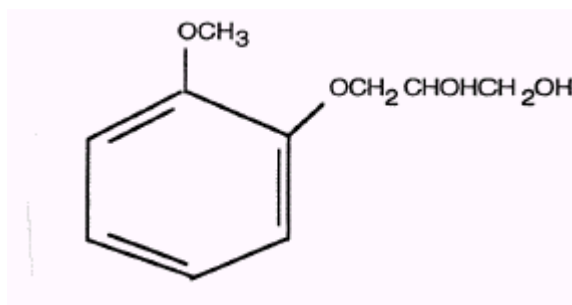
Non-medicinal ingredients in alphabetical order: alcohol, artificial coloring and flavoring, caramel, citric acid, FD&C yellow #6, glycerine, menthol, propylene glycol, purified water, sodium benzoate, sodium citrate dehydrate, sodium cyclamate and sucrose. Alcohol: 4.1 % v/v. Sucrose: 45 %. Bottles of 500 mL and 1 L.

PHARMACEUTICAL INFORMATION**Drug substance:****Guaifenesin**

Chemical name:

3-(2-Methoxyphenoxy)-1,2-propanediol.

Structure formula:



Molecular formula:

C₁₀H₁₄O₄

C 60.59%; H 7.12%; O 32.29%

Description:

Molecular weight:

198.21

Physical form:

White to slightly grey, crystals or crystalline aggregates, odourless.

Solubility:

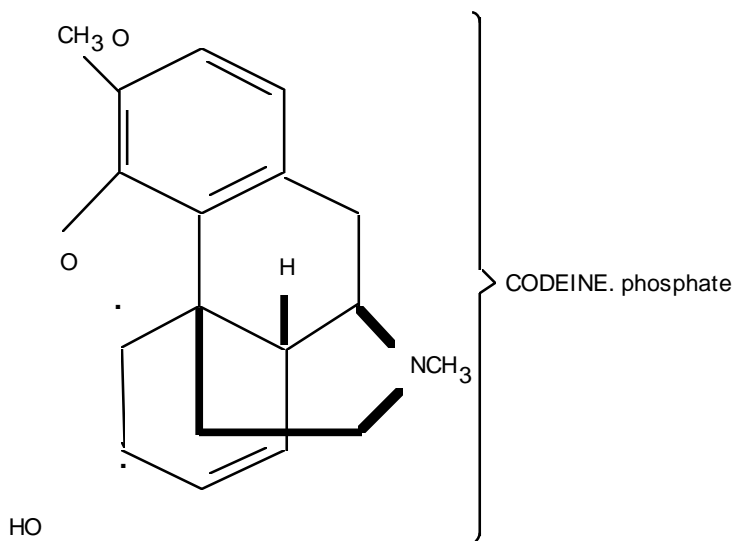
Soluble 1 in 60 to 70 of water. A 1% solution in water has a pH 5 to 7. Also soluble in alcohol.

Drug substance:**Codeine Phosphate**

Chemical name:

Morphinan-6-ol, 7, 8-didehydro-4,5-epoxy-3-methoxy-17-methyl, (5 alpha, 6 alpha)-, phosphate (1:1).

Structure formula:



Molecular formula:

C₁₈H₂₄NO₇P

C 54.41%, H 6.09%, N 3.53%, O 28.18%, P 7.79%

Description:

Molecular weight:

397.37

Physical form:

Fine, white, needle-shaped crystals, or white, crystalline powder. Is odourless, and is affected by light. Its solutions are acid to litmus.

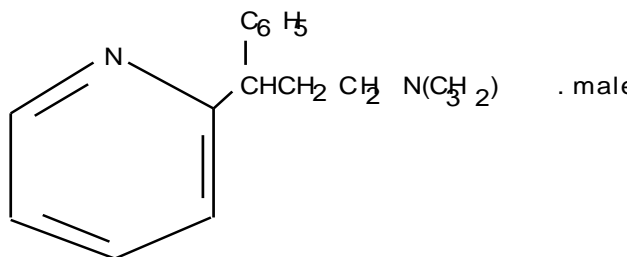
Solubility:

Freely soluble in water; very soluble in hot water; slightly soluble in alcohol but more so in boiling alcohol.

Drug substance: **Pheniramine Maleate**

Chemical name: N,N-dimethyl-g-phenyl-2-pyridine-propanamine maleate.

Structure formula:



Molecular formula: C₂₀H₂₄N₂O₄

Description:

Molecular weight: 356.4

Physical form: A white or almost white crystalline powder odourless or with a slight odour.

Solubility: Soluble 1 in 0.3 of water, 1 in 2.5 of alcohol, and 1 in 1.5 of chloroform; very slightly soluble in ether.

REFERENCE

1. Prescribing Information for ^NROBITUSSIN AC by Pfizer Consumer Healthcare, dated June 28, 2013, Control 165368.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals or 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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