

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>N</sup>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/ Antitussive/ Antihistamine**

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## TABLE OF CONTENTS

<b>PART I: HEALTH PROFESSIONAL INFORMATION .....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE .....	3
CONTRAINDICATIONS.....	4
WARNINGS AND PRECAUTIONS .....	5
ADVERSE REACTIONS .....	11
DRUG INTERACTIONS.....	12
DOSAGE AND ADMINISTRATION .....	12
OVERDOSAGE .....	14
ACTION AND CLINICAL PHARMACOLOGY .....	14
STORAGE AND STABILITY.....	16
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	16
<b>PART II: SCIENTIFIC INFORMATION.....</b>	<b>17</b>
PHARMACEUTICAL INFORMATION .....	17
REFERENCE .....	20
<b>PATIENT MEDICATION INFORMATION.....</b>	<b>21</b>

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**Expectorant/ Cough Suppressant/ Antihistamine**

### PART I: HEALTH PROFESSIONAL INFORMATION

#### 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

##### Adults

CALMYLIN ACE is indicated for temporary expectoration and control cough associated with inflamed mucosa.

##### Geriatrics (> 65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

##### Pediatrics (< 18 years of age)

Regardless of clinical setting, codeine (including CALMYLIN ACE) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**; also **DOSAGE AND ADMINISTRATION**)

The safety and efficacy of Guaifenesin, Codeine Phosphate, and Pheniramine Maleate has not been studied in the pediatric population. Therefore the use of CALMYLIN ACE is not recommended in patients over 12 and under 18 years of age.

## CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance codeine, guaifenesin, pheniramine or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- CYP2D ultra-rapid metabolizers who convert codeine into its active metabolite more rapidly and completely than other people (see **WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine; SYMPTOMS AND TREATMENT OF OVERDOSAGE, Codeine**)
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

- Women who are breast-feeding, and during pregnancy, or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS**, and **WARNINGS AND PRECAUTIONS**).

## WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

#### **Limitations of Use**

**Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with controlled release opioid formulations**, CALMYLIN ACE should only be used in patients for whom alternative non-opioid treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate cough management (see **DOSAGE AND ADMINISTRATION**).

#### **Addiction, Abuse, and Misuse**

CALMYLIN ACE poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing CALMYLIN ACE, and all patients should be monitored regularly for the development of these behaviours or conditions (see **WARNINGS AND PRECAUTIONS**). CALMYLIN ACE should be stored securely to avoid theft or misuse.

#### **Life-threatening Respiratory Depression: OVERDOSE**

Serious, life-threatening, or fatal respiratory depression may occur with use of CALMYLIN ACE. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of CALMYLIN ACE or following a dose increase.

#### **Accidental Exposure**

Accidental exposure to CALMYLIN ACE, especially by children, can result in a fatal overdose of CALMYLIN ACE (see **DOSAGE AND ADMINISTRATION, Disposal**, for instructions on proper disposal).

#### **Neonatal Opioid Withdrawal Syndrome**

Prolonged maternal use of CALMYLIN ACE during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see **WARNINGS AND PRECAUTIONS**).

### **Interaction with Alcohol**

**The co-ingestion of alcohol with CALMYLIN ACE should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).**

### **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 AND PRECAUTIONS).**

- **Reserve concomitant prescribing of CALMYLIN ACE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

### **General**

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

**Accidental ingestion, especially by children can result in a fatal overdose of codeine (see DOSAGE AND ADMINISTRATION, disposal, for instructions on proper disposal).**

**Patients should be instructed not to give CALMYLIN ACE to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. CALMYLIN ACE should be stored securely to avoid theft or misuse.**

Patients should be cautioned not to consume alcohol while taking CALMYLIN ACE as it may increase the chance of experiencing serious adverse events, including death. 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.

Patients should be counselled to discontinue codeine products and to seek urgent medical help at the earliest sign of codeine toxicity including symptoms such as confusion, shallow breathing, or extreme sleepiness which may be life threatening.

### **Abuse and Misuse**

Like all opioids, CALMYLIN ACE is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, CALMYLIN ACE should be prescribed and handled with

caution. Opioids, such as **CALMYLIN ACE** should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse.

### **Endocrine**

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

### **Cardiovascular**

Codeine administration may result in hypotension and dizziness. Use with caution in patients with cardiac arrhythmias due to the cholinergic effects of the drug.

### **Dependence/Tolerance**

As with other opioids, tolerance and physical dependence may develop upon repeated administration of CALMYLIN ACE and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

### **Use in Drug and Alcohol Addiction**

CALMYLIN ACE is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of cough requiring an opioid. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to CALMYLIN ACE; extreme caution and awareness is warranted to mitigate the risk.

### **Gastrointestinal Effects**

Codeine and other morphine-like opioids have been shown to decrease bowel motility. Codeine may obscure the diagnosis or clinical course of 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.

### **Neonatal Opioid Withdrawal Syndrome (NOWS)**

Use of CALMYLIN ACE is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

### **Neurologic**

**Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol):** Concomitant use of opioids, including CALMYLIN ACE, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, 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 **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 CALMYLIN ACE is used with benzodiazepines, alcohol, or other CNS depressants.

**Head Injury:** The respiratory depressant effects of codeine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, codeine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, codeine must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

### **Risk of Death in 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 labelled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. (See also **Labour, Delivery and Nursing Women in Special Populations**).

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 **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

### **Peri-Operative Considerations**

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.

**Serotonin Syndrome:** CALMYLIN ACE could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. CALMYLIN ACE should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

### **Psychomotor Impairment**

CALMYLIN ACE may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of Codeine with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

### **Respiratory**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. CALMYLIN ACE should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of CALMYLIN ACE, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with CALMYLIN ACE and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

**Codeine:** Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome (see **CONTRAINDICATIONS**).

**Use in Patients with Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with CALMYLIN ACE, as in these patients, even usual therapeutic doses of CALMYLIN ACE may decrease respiratory drive to the point of apnea. The use of CALMYLIN ACE is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

**Sexual Function/Reproduction:** Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

### **Special Populations**

**Special Risk Groups:** Codeine should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, glaucoma, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

**Pregnant Women:** Studies in humans have not been conducted. CALMYLIN ACE crosses the placental barrier and is contraindicated in pregnant women. Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

**Labour, Delivery and Nursing Women:** Since opioids can cross the placental barrier and are excreted in breast milk, CALMYLIN ACE is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if CALMYLIN ACE is used in this population.

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. **However, some women are ultra-rapid metabolisers of codeine (see CONTRAINDICATIONS, Ultra-Rapid Metabolisers of Codeine; and WARNINGS AND PRECAUTIONS, Risk of Death in 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 breast-fed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.**

Since there is a risk of infant exposure to codeine and morphine through breast milk, CALMYLIN ACE is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

**Pediatrics (< 18 years of age):** Regardless of clinical setting, codeine (including CALMYLIN ACE) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see INDICATIONS, and DOSAGE AND ADMINISTRATION). CALMYLIN ACE may cause drowsiness or excitability, especially in children. The safety and efficacy of Guaifenesin, Codeine Phosphate, and Pheniramine Maleate have not been studied in the pediatric population. Therefore, use of CALMYLIN ACE is not recommended in patients under 18 years of age.

**Geriatrics (> 65 years of age):** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

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.

## **Post-marketing Experience**

### **Spontaneously Reported Adverse Events for guaifenesin, codeine phosphate and pheniramine maleate**

The following events were reported singly; Condition aggravated, Cough, Drug hypersensitivity, Drug ineffective, Insomnia and Overdose, while Somnolence was reported twice.

**Androgen deficiency:** Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

## **DRUG INTERACTIONS**

### **Overview**

**Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants (including alcohol):** Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death and should be avoided (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). CALMYLIN ACE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Coadministration of Codeine Phosphate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

### **Drug-Lifestyle Interactions**

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

## **DOSAGE AND ADMINISTRATION**

**Children under 12:** Regardless of clinical setting, codeine (including CALMYLIN ACE) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **INDICATIONS**)

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. The maximum recommended daily dose of CALMYLIN ACE is 60 mL, which is 120 mg codeine (18 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing CALMYLIN ACE, as the likelihood of experiencing serious adverse events can depend upon the type of opioid and duration of treatment, as well as the patient's own level of tolerance. In addition, the coughing should be assessed routinely to confirm the most appropriate dose and the need for further use of CALMYLIN ACE.

### **Considerations**

CALMYLIN ACE may be taken with or without food, with a glass of water.

### **Recommended Dose and Dosage Adjustment**

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.

### **Adults**

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.

### **Geriatrics:**

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. CALMYLIN ACE should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

**Adjustment or Reduction of Dosage:** Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including CALMYLIN ACE. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy.

These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

### **Missed Dose**

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take two doses at the same time.

### **Disposal**

CALMYLIN ACE should be kept in a safe place, out of the sight and reach of children before, during and after use. CALMYLIN ACE should not be used in front of children, since they may copy these actions.

**CALMYLIN ACE should never be disposed of in household trash.** Disposal via a pharmacy take back program is recommended. Unused or expired CALMYLIN ACE should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

### **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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### **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.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

#### **Endocrine System:**

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

### **Mechanism of Action**

**Codeine Phosphate:** Codeine is a narcotic analgesic which binds to the mu receptor as an opiate receptor agonist. Although the exact mechanism of analgesic action is unknown, it may come from its conversion to morphine. Codeine is also associated with antitussive effects via direct depression of the medullary cough reflex.

**Pheniramine Maleate:** Pheniramine is an alkylamine derivative which is a potent H<sub>1</sub> antagonist. Its actions are mediated by reversible and competitive inhibition of the interaction of histamine with H<sub>1</sub> receptors on cells, preventing histamine effects on target organs.

**Guaifenesin:** Guaifenesin is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. Thus, it may increase the efficiency of the cough reflex and facilitate removal of the secretions. However, objective evidence for this is limited and conflicting

## **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.



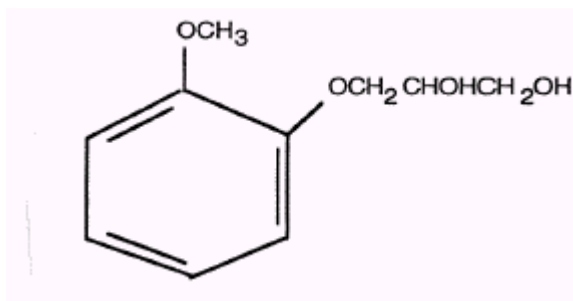
## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

**Drug substance:** Guaifenesin

Chemical name: 3-(2-Methoxyphenoxy)-1,2-propanediol.

Structure formula:



Molecular formula: C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>

**Description:**

Molecular weight: 198.21 g/mol

Physical form: White to slightly grey, crystals or crystalline aggregates, odourless.

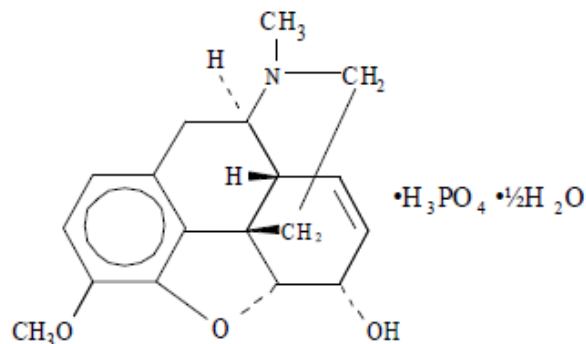
Solubility: Soluble 1 in 60 to 70 of water. A 1% solution in water has a pH 5 to 7. Also soluble in alcohol.

**Drug substance:****Codeine Phosphate**

Chemical name:

7, 8-didehydro-4,5 $\alpha$ -epoxy-3-methoxy-17- methylmorphinan-6 $\alpha$ -ol-phosphate (1:1) (salt) hemihydrate

Structure formula:



Molecular formula:

 $\text{C}_{18}\text{H}_{21}\text{NO}_3 \cdot \text{H}_3\text{PO}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$ **Description:**

Molecular weight:

406.4 g/mol

Physical form:

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

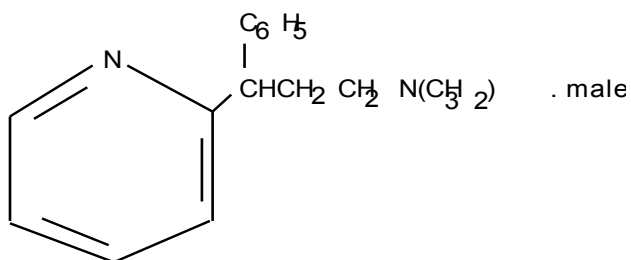
Solubility:

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-3-phenyl-3-(2-pyridyl)-propanamine maleate (1:1).

Structure formula:



Molecular formula:                      C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>

**Description:**

Molecular weight:                      356.4 g/mol

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 <sup>N</sup>ROBITUSSIN<sup>®</sup> AC by Pfizer Consumer Healthcare, dated August 15, 2018, Control 213752.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**<sup>N</sup>CALMYLIN ACE**

Guafenesin, Codeine Phosphate and Pheniramine Maleate Syrup

Read this carefully before you start taking **CALMYLIN ACE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CALMYLIN ACE**.

**Serious Warnings and Precautions**

- **Even if you take CALMYLIN ACE as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life threatening breathing problems while taking CALMYLIN ACE. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your CALMYLIN ACE. They could die from taking it. If a person has not been prescribed CALMYLIN ACE, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took CALMYLIN ACE while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**

**Taking CALMYLIN ACE with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

**What is CALMYLIN ACE used for?**

CALMYLIN ACE is used for the temporary relief, in adults, of dry coughs, chest congestion, runny nose and sneezing associated with:

- the common cold

**How does CALMYLIN ACE work?**

Codeine Phosphate acts on the brain to suppress cough.

Guafenesin helps relieve chest congestion.

Pheniramine Maleate helps relieve runny nose and sneezing.

**What are the ingredients in CALMYLIN ACE?**

Medicinal ingredients: Guaifenesin, Codeine Phosphate and Pheniramine Maleate

Non-medicinal ingredients: 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 %.

**CALMYLIN ACE comes in the following dosage forms:**

Syrup, each 5 mL of which contains: guaifenesin 100 mg, codeine phosphate 10 mg and pheniramine maleate 7.5 mg

**Do not use CALMYLIN ACE if you:**

- your doctor did not prescribe it for you
- are allergic to guaifenesin, codeine phosphate and pheniramine maleate or to any of the other ingredients in CALMYLIN ACE
- feel sedated, drowsy or confused
- have severe asthma, trouble breathing, or other breathing problems
- have bowel blockage or narrowing of the stomach or intestines
- have a head injury
- are at risk for having seizures
- suffer from alcoholism
- are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose.
- are pregnant or planning to become pregnant or you are in labour
- are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take CALMYLIN ACE, seek immediate medical care for your baby if they are overly drowsy, sedated, have difficulty breast-feeding, have breathing difficulties, and are floppy (have decreased muscle tone). This is very serious for the baby and can lead to death. Tell the baby's doctor that you are breastfeeding and took CALMYLIN ACE
- you are less than 18 years old and are having (or have recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep
- you are less than 12 years old

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CALMYLIN ACE. Talk about any health conditions or problems you may have, including if you:**

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have low blood pressure
- have past or current depression

- suffer from chronic or severe constipation
- have persistent or chronic cough (as occurs with smoking), glaucoma, high blood pressure, heart disease
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- or under a physician's care

**Other warnings you should know about:**

**Some people metabolize codeine at a much faster rate than the general population, which may lead to accidental overdose, if this should happen to you, seek help immediately (see Overdose, for symptoms of overdose and what to do if it happens). If you know that you metabolize codeine rapidly, tell your doctor BEFORE starting this medication.**

CALMYLIN ACE is not recommended for anyone who has or is at risk for breathing problems such as:

- lung infections, or respiratory conditions
- neuromuscular disorders
- severe heart problems
- recent multiple traumas or extensive surgical procedures

**Opioid dependence and addiction:**

**There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have any questions or concerns about abuse, addiction or physical dependence. As with all opioids, taking guaifenesin, codeine phosphate and pheniramine maleate may cause you to become dependent on it. Do not take more than the dose prescribed to you by your doctor.**

**Pregnancy, nursing, labour and delivery:**

Do not use CALMYLIN ACE while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. CALMYLIN ACE can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking CALMYLIN ACE, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking CALMYLIN ACE. This may help avoid serious harm to your unborn baby.

**Driving and using machines:** Before you do tasks which may require special attention, you should wait until you know how you react to CALMYLIN ACE. CALMYLIN ACE can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

**Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones.

You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off CALMYLIN ACE.

**Serotonin Syndrome:** Codeine, one of the ingredients of CALMYLIN ACE can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take CALMYLIN ACE with certain antidepressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness and coma.

**Sexual Function/Reproduction:** Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with CALMYLIN ACE:**

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking CALMYLIN ACE. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by CALMYLIN ACE
- opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)



- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take CALMYLIN ACE with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs to treat allergies)
- antitussives
- decongestants
- expectorants
- anti-emetics (drugs used to prevent vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin (such as coumadin) and other anticoagulants (used to prevent or treat blood clots)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta blockers)
- tranquilizers, sedatives, sedating antihistamines, other depressants, other salicylates
- drugs used to treat migraines (eg. triptans)
- grapefruit juice
- St. John's Wort

### **How to take CALMYLIN ACE:**

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take **CALMYLIN ACE** for up to 7 days. If you need to take **CALMYLIN ACE** for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

### **Usual Dose:**

Take every 4–6 hours or as directed by a physician. Maximum 6 doses daily (60 mL).

Adults: 2 teaspoons (10 mL)

Children under 12 years: **DO NOT USE**

### **Stopping your Medication**

If you have been taking **CALMYLIN ACE** for more than a few days, you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking **CALMYLIN ACE**. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea

- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking CALMYLIN ACE.

### **Refilling your Prescription for CALMYLIN ACE**

A new written prescription is required from your doctor each time you need more CALMYLIN ACE. Therefore, it is important that you contact your doctor before your current supply runs out. Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your illness.

### **Overdose:**

If you think you have taken too much CALMYLIN ACE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

### **Missed Dose:**

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take two doses at the same time.

### **What are possible side effects from using CALMYLIN ACE?**

These are not all the possible side effects you may feel when taking CALMYLIN ACE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

<b>Serious side effects and what to do about them</b>				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
<b><u>RARE</u></b>	<b>Overdose:</b> hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			✓
	<b>Respiratory Depression:</b> Slow, shallow or weak breathing.			✓
	<b>Allergic Reaction:</b> rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	<b>Bowel Blockage (impaction):</b> abdominal pain, severe constipation, nausea			✓

<b>Fast, Slow or Irregular Heartbeat:</b> heart palpitations.		✓	
<b>Low Blood Pressure:</b> dizziness, fainting, lightheadedness.	✓		
<b>Serotonin Syndrome:</b> agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

- **Keep unused or expired CALMYLIN ACE in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature (15°-30°C).
- **Keep CALMYLIN ACE under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes CALMYLIN ACE, get emergency help right away.**

### Disposal:

**CALMYLIN ACE should never be thrown into household trash, where children and pets may find it.** It should be returned to a pharmacy for proper disposal.

### If you want more information about CALMYLIN ACE:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website; (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.tevacanada.com>; or by calling 1-800-268-4127 ext. 3; or email [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com).

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