PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

NROBITUSSIN® AC

Guaifenesin, Codeine Phosphate and Pheniramine Maleate Syrup
20 mg / 2 mg / 1.5 mg: per mL of syrup

Expectorant/Antitussive/Antihistamine

GlaxoSmithKline Consumer Healthcare ULC
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Mississauga, Ontario
L5N 6L4

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[N]ROBITUSSIN® AC

Guaifenesin, Codeine Phosphate and Pheniramine Maleate Syrup

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Syrup, each mL of which contains: guaifenesin 20 mg, codeine phosphate 2 mg and pheniramine maleate 1.5 mg	Alcohol, caramel colour, citric acid, FD&C Red No. 40, FD&C Yellow No. 6, glycerin, invert sugar, menthol flavour, purified water, raspberry flavours and sodium benzoate

INDICATIONS AND CLINICAL USE

Adults
Robitussin® AC 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.

Pediatrics (< 18 years of age)
Robitussin® AC is not indicated for use in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and because the benefits of symptomatic treatment of cough do not outweigh the risks for use of codeine in these patients (see also **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

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, diabetes, heart or thyroid disease or glaucoma.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- CYP2D6 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 <12 years of age.
- 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, Robitussin® AC 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

Robitussin® AC 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 Robitussin® AC, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Robitussin® AC should be stored securely to avoid theft or misuse.

SERIOUS WARNINGS AND PRECAUTIONS

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression including central sleep apnoea (CSA) and sleep-related hypoxemia may occur with use of Robitussin® AC. 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 Robitussin® AC or following a dose increase.

Accidental Exposure

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

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of Robitussin® AC 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 Robitussin® AC 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 Robitussin® AC 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 Robitussin® AC to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Robitussin® AC should be stored securely to avoid theft or misuse.

Patients should be cautioned not to consume alcohol while taking Robitussin® AC as it may increase the chance of experiencing serious adverse events, including death. Patients should be advised to 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, **Robitussin® AC** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **Robitussin® AC** should be prescribed and handled with caution.

Opioids, such as **Robitussin® AC**, 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 Robitussin® AC 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

Robitussin® AC 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 Robitussin® AC; 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 Robitussin® AC 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 Robitussin® AC, 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 Robitussin® AC 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 toxicity / Serotonin syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported during use of opioids such as Robitussin® AC, particularly during combined use with other serotonergic drugs (see DRUG INTERACTIONS).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

If concomitant treatment with Robitussin® AC and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see DRUG INTERACTIONS). If serotonin toxicity is suspected, a temporary discontinuation of one or more of the likely causative agents for the serotonin toxicity should be considered.

Psychomotor Impairment
Robitussin® AC 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. Robitussin® AC 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 Robitussin® AC, 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 Robitussin® AC 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.

Risk Factors for Life-threatening Respiratory Depression in Children:
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).

- Codeine-containing products are contraindicated for all children younger than 12 years of age.
- Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome (see CONTRAINDICATIONS).
- Avoid the use of codeine-containing products in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

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 Robitussin® AC, as in these patients, even usual therapeutic doses of Robitussin® AC may decrease respiratory drive to the point of apnea. The use of Robitussin® AC is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sleep Apnea

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the Robitussin® AC treatment if appropriate, using best practices for tapering of opioids (see WARNINGS AND PRECAUTIONS, Dependence/Tolerance; DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Robitussin® AC requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine. (See **DRUG INTERACTIONS)**

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 (see **ADVERSE REACTIONS, Post-Marketing Experience**).

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. Robitussin® AC 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**).

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, Robitussin® AC 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 Robitussin® AC 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, Robitussin® AC 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): Robitussin® AC is not indicated for use in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and because the benefits of symptomatic treatment of cough do not outweigh the risks for use of codeine in these patients (see **INDICATIONS, CONTRAINDICATIONS**, and **DOSAGE AND ADMINISTRATION**).

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**).

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 ^{N}ROBITUSSIN® AC (guaifenesin, codeine phosphate and pheniramine maleate)

Since the inception of marketing **[N]ROBITUSSIN® AC,** (combination product Guaifenesin, Codeine Phosphate and Pheniramine Maleate**)** Pfizer has received 5 cases describing 8 adverse events. 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**). Robitussin® AC should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Interaction with Serotonin:
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).**

MAO Inhibitors
Serious adverse reactions have been reported in patients who receive MAO inhibitors with pethidine. Other opioid analgesics should be used with extreme caution, if at all, in patients taking MAO inhibitors (including selegiline) or within 14 days of such therapy.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The effects of concomitant use or discontinuation of CYP3A4 inducers, CYP3A4 inhibitors, or CYP2D6 inhibitors with codeine are complex, and requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

Avoid the use of Robitussin® AC while taking CYP3A4 inducers, CYP3A4 inhibitors, or

CYP2D6 inhibitors. If concomitant use is necessary, monitor patients for respiratory depression and sedation at frequent intervals or for signs of opioid withdrawal.

CYP3A4 inhibitors: The concomitant use of Robitussin® AC and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), or protease inhibitors (e.g., ritonavir) can increase the plasma concentration of codeine and its subsequent metabolism by CYP2D6, resulting in greater morphine levels, which could increase or prolong opioid effects. The discontinuation of a concomitantly used CYP3A4 inhibitor might results in a reduced efficacy of Robitussin® AC.

CYP2D6 inhibitors: The concomitant use of Robitussin® AC and CYP2D6 inhibitors (e.g., amiodarone, quinidine) may result in a decrease in active metabolite morphine plasma concentration, leading to decreased efficacy or symptoms of opioid withdrawal. The discontinuation of a concomitantly used CYP2D6 inhibitor may lead to an increased metabolism to morphine, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

CYP3A4 inducers: The concomitant use of Robitussin® AC and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, may result in a decreased plasma concentration of codeine and its active metabolite morphine, leading to decreased efficacy or symptoms of opioid withdrawal. The discontinuation of a concomitantly used CYP3A4 inducer can increase the plasma concentration of codeine and its active metabolite morphine which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Pediatrics (under 18 years)

Robitussin® AC is not indicated for use in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine and because the benefits of symptomatic treatment of cough do not outweigh the risks for use of codeine in these patients.

Increasing Risk with Higher Doses

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 Robitussin AC is 60 mL, which is 120 mg codeine (18 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing Robitussin AC, 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 Robitussin AC.

Considerations
Robitussin® AC may be taken with or without food, with a glass of water.

Recommended Dose and Dosage Adjustment
Codeine, including Robitussin AC, 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 teaspoons) every 4 to 6 hours as follows or as directed by a doctor. Do not exceed 6 doses (12 teaspoons) 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. Robitussin® AC should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS**).

Adjustment or Reduction of Dosage: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Robitussin® AC. 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
Robitussin® AC should be kept in a safe place, out of the sight and reach of children before, during and after use. Robitussin® AC should not be used in front of children, since they may copy these actions.

Robitussin® AC should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Robitussin® AC 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.

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 H1 antagonist. Its actions are mediated by reversible and competitive inhibition of the interaction of histamine with H1 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

Robitussin® AC should be stored at room temperature (15-30°C).

Others:

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

Each mL of orange, cherry-flavored syrup contains: guaifenesin 20 mg, codeine phosphate 2 mg and pheniramine maleate 1.5 mg.

Nonmedicinal ingredients: alcohol, caramel colour, citric acid, FD&C Red No. 40, FD&C Yellow No. 6, glycerin, invert sugar, menthol flavour, purified water, raspberry flavours and sodium benzoate.

Energy: 2.78 kcal / mL. Sodium: 0.16 mg / mL. Gluten-, parabens- and tartrazine (FD&C Yellow No. 5)-free.

Packaging:
Bottles of 1 L.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:
Guaifenesin
Codeine Phosphate
Pheniramine Maleate

Chemical name:
Guaifenesin:

IUPAC Name: (*RS*)-3-(2-methoxyphenoxy)propane-1,2-diol
CAS Name: 3-(2-Methoxyphenoxy)-1,2-propanediol
Additional Names: glycerol mono(2-methoxyphenyl) ether; glycerol α-(2-methoxyphenyl) ether; guaiacyl glyceryl ether; glyceryl guaiacyl ether; glycerol guaiacolate; α-glyceryl guaiacol ether; *o*-methoxyphenyl glyceryl ether; 1,2-dihydroxy-3-(2-methoxyphenoxy)propane; guaiacol glyceryl ether; guaiphenesin; guaiacuran

Codeine:

IUPAC Name: (4R,4aR,7S,7aR,12bS)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7-ol
CAS Name: (5α,6α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol
Additional Names: methylmorphine; morphine monomethyl ether; morphine 3-methyl ether

Pheniramine Maleate:

IUPAC Name: (Z)-but-2-enedioic acid;N,N-dimethyl-3-phenyl-3-pyridin-2-ylpropan-1-amine

Molecular formula and molecular mass:
Guaifenesin:

Molecular Formula: $C_{10}H_{14}O_4$

Molecular Weight: 198.22

Codeine:

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

Molecular Weight: 299.36

Codeine Phosphate:

Molecular Formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4$

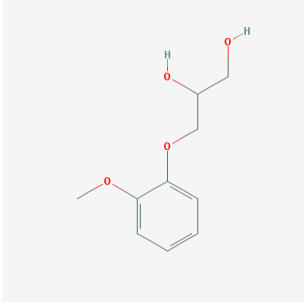
Molecular Weight: 397.36

Pheniramine Maleate:

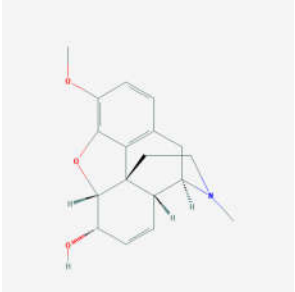
Molecular Formula: $C_{16}H_{20}N_2 \cdot C_4H_4O_4$

Molecular Weight: 356.42

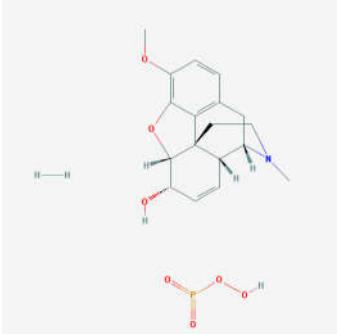
Structural formula:
Guaifenesin:



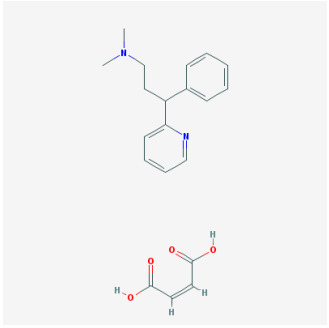
Codeine:



Codeine Phosphate:



Pheniramine Maleate:



Physicochemical Properties:
Guaifenesin: Crystals, melting point 132-134 °C. Freely soluble in water; soluble in alcohol, chloroform. pH of a 2% aqueous solution about 5. Slightly soluble in ether, benzene.

Codeine Phosphate: Fine, white, needle-shaped crystals or crystalline powder. Odorless; affected by light. Solutions acidic to litmus. Freely soluble in water; very soluble in hot water; slightly soluble in alcohol; more soluble in boiling alcohol.

Pheniramine Maleate: Crystals from amyl alcohol, faint amine-like odor, melting point 107 °C. Soluble in water, alcohol; slightly soluble in ether, benzene. pH of 1% aqueous solution between 4.3 and 4.9.

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

^{N}ROBITUSSIN® AC

Guaifenesin, Codeine Phosphate and Pheniramine Maleate Syrup

Read this carefully before you start taking **Robitussin® AC** 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 **Robitussin® AC**.

Serious Warnings and Precautions

- **Even if you take Robitussin® AC 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 Robitussin® AC. 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 Robitussin® AC. They could die from taking it. If a person has not been prescribed Robitussin® AC, taking even one dose can cause a fatal overdose. This is especially true for children.**

- **If you took Robitussin® AC 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 Robitussin® AC 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 Robitussin® AC used for?

Robitussin® AC is used for the temporary relief, in adults, of dry coughs, chest congestion, runny nose and sneezing associated with*:*

- the common cold

Robitussin® AC is not for use in patients younger than 18 years of age. In patients this age, the risks of life-threatening breathing problems outweigh the benefits of treating the cough with codeine.

How does Robitussin® AC work?
Codeine Phosphate acts on the brain to supress cough.
Guaifenesin helps relieve chest congestion.
Pheniramine Maleate helps relieve runny nose and sneezing.

What are the ingredients in Robitussin® AC?
Medicinal ingredients: Guaifenesin, Codeine Phosphate and Pheniramine Maleate

Non-medicinal ingredients: Alcohol, caramel colour, citric acid, FD&C Red No. 40, FD&C Yellow No. 6, glycerin, invert sugar, menthol flavour, purified water, raspberry flavour and sodium benzoate

Robitussin® AC comes in the following dosage forms:
Syrup, each mL of which contains: guaifenesin 20 mg, codeine phosphate 2 mg and pheniramine maleate 1.5 mg

Do not use Robitussin® AC 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 Robitussin® AC
- have severe asthma, trouble breathing, or other breathing problems
- you have acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale
- have bowel blockage or narrowing of the stomach or intestines
- have a head injury
- are at risk for having seizures

- have diabetes
- have heart or thyroid problems
- have glaucoma
- 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 Robitussin® AC, 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 Robitussin® AC

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Robitussin® AC. 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), high blood pressure
- have a history of sleep apnea
- have problems with your adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- are under a physician's care

Other warnings you should know about:

Some people metabolize codeine at a much faster rate than the general population. This may lead to accidental overdose. Stop taking Robitussin® AC and seek immediate medical help if you start feeling confused, have shallow breathing, or extreme sleepiness. If you know that you metabolize codeine at a much faster rate, tell your doctor BEFORE starting this medication.

Stop taking Robitussin® AC and consult with your healthcare professional if:

- you get a high fever, rash or persistent headache along with the cough.
- your symptoms or cough worsen or continue for more than 7 days.

These could be signs of a serious condition.

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 codeine 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 Robitussin® AC while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. Robitussin® AC can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking Robitussin® AC, 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 Robitussin® AC. 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 Robitussin® AC. Robitussin® AC 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 Robitussin® AC.

Serotonin Syndrome: Codeine, one of the ingredients of Robitussin® AC 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 Robitussin® AC with certain antidepressants or migraine medications.

Serotonin Syndrome symptoms include:

- involuntary eye movements
- fever (>38°C), heavy sweating, flushing, 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.

Sleep apnea
Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your doctor if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

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 Robitussin® AC:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Robitussin® AC. 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 Robitussin® AC
- 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 Robitussin® AC 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
- some anti-retroviral drugs (used to treat viral infections)
- some anti-fungal drugs (used to treat fungal infections)
- some 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 Robitussin® AC:

- Your doctor will prescribe the lowest dose that works to control your symptoms.
- It is recommended that you only take Robitussin® AC for up to 7 days. If you need to take Robitussin® AC 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.
- Robitussin® AC may be taken with or without food, with a glass of water.

Usual Dose:

Take every 4–6 hours or as directed by a physician. Maximum 6 doses daily (60 mL).
Adults : 2 teaspoons (10 mL)

Stopping your Medication
If you have been taking Robitussin® AC 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 Robitussin® AC. 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 Robitussin® AC.

Refilling your Prescription for Robitussin® AC

A new written prescription is required from your doctor each time you need more Robitussin® AC. 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 Robitussin® AC, 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 Robitussin® AC?
These are not all the possible side effects you may feel when taking Robitussin® AC. 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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE: **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin			✓
Respiratory Depression: Slow, shallow or weak breathing			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations		✓	
Low Blood Pressure: dizziness, fainting, light-headedness	✓		
Serotonin Syndrome: 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 Robitussin® AC in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep Robitussin® AC 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 Robitussin® AC, get emergency help right away.**
- Store at room temperature (15°-30°C).

Disposal:

Robitussin® AC 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 Robitussin® AC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer 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), or by calling the sponsor, GlaxoSmithKline Consumer Healthcare ULC, Mississauga, Ontario L5N 6L4 at 1-888-275-9938.

This leaflet was prepared by GlaxoSmithKline Consumer Healthcare ULC

Last Revised: October 8, 2020