PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]ROBAXISAL® C ½

(methocarbamol, codeine phosphate and acetylsalicylic acid)

400 mg/32.4 mg/325 mg: per tablet

Skeletal Muscle Relaxant/Analgesic

GlaxoSmithKline Consumer Healthcare ULC
55 Standish Court, suite 450
Mississauga, ON
L5R 4B2

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[N]ROBAXISAL® C ½

(methocarbamol, codeine phosphate and acetylsalicylic acid (ASA)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet, each of which contains: methocarbamol 400 mg, ASA 325 mg and codeine phosphate 32.4 mg	Cellulose, cornstarch, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, magnesium stearate, polyethylene glycol, povidone, sodium starch glycolate and stearic acid.

INDICATIONS AND CLINICAL USE

Adults

Robaxisal C ½ (methocarbamol, codeine phosphate and ASA) is indicated for moderate pain due to or associated with skeletal muscle spasm: acute torticollis, acute strains and sprains, acute low back pain, acute tenosynovitis, ankle sprain, fracture, trauma, acute bursitis, acute myositis, whiplash injury.

Robaxisal C ½ is not indicated as an as-needed (prn) analgesic.

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 (< 12 years of age)

Regardless of clinical setting, codeine (including Robaxisal C ½) 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**; and **DOSAGE AND ADMINISTRATION**).

The safety and efficacy of Robaxisal C ½ has not been studied in the pediatric population. Therefore, the use of Robaxisal C ½ is not recommended in patients over 12 years and under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance methocarbamol, ASA, codeine, 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 suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- 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.
- 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** and **OVERDOSAGE**).
- 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, Special Populations, Pregnant Women**).
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.
- Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage).
- Patients who have had a bronchospastic reaction, generalized urticaria, angioedema, severe rhinitis, laryngeal edema, or shock precipitated by ASA or nonsteroidal anti-inflammatory drugs. Some patients sensitive to ASA, may be cross-sensitive to other nonsteroidal anti-inflammatory drugs as well as tartrazine dye. Patients with asthma associated nasal polyps have an increased risk of sensitivity to ASA.
- Patients with active peptic ulcer or other serious gastrointestinal lesions.
- **Children, teenagers, and young adults with varicella or influenza, unless directed by a physician.**

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 risks of overdose and death with immediate release opioid formulations, Robaxisal C ½ (methocarbamol, codeine phosphate and ASA tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

Robaxisal C ½ 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 Robaxisal C ½, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Robaxisal C ½ should be stored securely to avoid theft or misuse.

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 Robaxisal C ½. 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 Robaxisal C ½ or following a dose increase.

Robaxisal C ½ (which contain codeine) must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Robaxisal C ½ can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of Robaxisal C ½, especially by children, can result in a fatal overdose of codeine phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Risk in Pregnancy

Robaxisal C ½ is contraindicated for use during pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see WARNINGS AND PRECAUTIONS). During the third trimester there is risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see also WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine, Neonatal Opioid Withdrawal Syndrome (NOWS), and Special Populations, Pregnant Women).

SERIOUS WARNINGS AND PRECAUTIONS

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Robaxisal C ½ 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 Robaxisal C ½ 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, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of Robaxisal C ½ 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
Patients should be instructed not to give Robaxisal C ½ tablets to anyone other than the patient for whom it was prescribed; as such inappropriate use may have severe medical consequences, including death. Robaxisal C ½ should be stored securely to avoid theft or misuse.

Robaxisal C ½ should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Robaxisal C ½ as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of codeine phosphate can occur at particularly high doses. A codeine phosphate dose reduction or change in opioid may be required (see **WARNINGS AND PRECAUTIONS, Opioid Induced Hyperalgesia**).

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.

ASA is one of the most frequent causes of accidental poisoning in toddlers and infants. ASA containing preparations should therefore be kept well out of the reach of all children.

Salicylates should be administered with caution to patients with asthma and other allergic conditions, with bleeding tendencies, or with hypoprothrombinemia or in patients prone to dyspepsia or known to have a lesion of the gastric mucosa. It should not be administered to patients with hemophilia or other hemorrhagic disorders or to those with intolerance to ASA (especially ASA-sensitive asthmatics). Caution is necessary when renal or hepatic function is impaired.

Salicylates can produce changes in the thyroid function tests.

ASA may precipitate or worsen attacks of gout.

ASA administered pre-operatively may prolong the bleeding time.

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 **WARNINGS AND PRECAUTIONS, Special Populations, Labour, Delivery and Nursing Women**).

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**).

Abuse and Misuse

Like all opioids, Robaxisal C ½ is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Robaxisal C ½ should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Robaxisal C ½, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Robaxisal C ½ is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Cardiovascular

Codeine phosphate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants, or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Robaxisal C ½.

The use of Robaxisal C ½ in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Robaxisal C ½ 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.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness, and yawning (see **ADVERSE REACTIONS** **and** **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Use in Drug and Alcohol Addiction: Robaxisal C ½ 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 pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Robaxisal C ½; extreme caution and awareness is warranted to mitigate the risk.

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 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.

Gastrointestinal Effects

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility. Codeine phosphate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Monitoring and Laboratory Tests

Pregnancy: Robaxisal C ½ is contraindicated for use in pregnancy. If Robaxisal C ½ is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on Robaxisal C ½ be closely monitored for amniotic fluid volume since Robaxisal C ½ may result in reduction of amniotic fluid volume and even oligohydramnios (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

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.

Use of Robaxisal C ½ is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Robaxisal C ½ should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, gabapentinoids, baclofen, centrally active anti-emetics, and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS

depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Robaxisal C ½ is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

Robaxisal C ½ should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS**, **ADVERSE REACTIONS, Sedation**, and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury: The respiratory depressant effects of codeine phosphate, 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 phosphate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, codeine phosphate must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

Opioid Induced Hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful stimuli (allodynia), in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

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 Robaxisal C ½, 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 Robaxisal C ½ 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.

Peri-Operative Considerations

Robaxisal C ½ is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Robaxisal C ½ for at least 24 hours before the operation and Robaxisal C ½ should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Robaxisal C ½ is to be continued after the patient recovers from the post-operative period; a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by health professionals with adequate training and experience (e.g., by an anesthesiologist).

Codeine phosphate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Robaxisal C ½ should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Robaxisal C ½ 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-phosphate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Life-Threatening Respiratory Depression: 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. Codeine phosphate 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 Robaxisal C ½, 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 Robaxisal C ½ 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.

To reduce the risk of respiratory depression, proper dosing, and titration of Robaxisal C ½ are essential. Overestimating the Robaxisal C ½ dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

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 Robaxisal C ½, as in these patients, even usual therapeutic doses of Robaxisal C ½ **may** decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Robaxisal C ½ 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 Robaxisal C ½ treatment if appropriate, using best practices for tapering of opioids (see **WARNINGS AND PRECAUTIONS, Dependence/Tolerance** and **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**, **Post-Marketing Experience**).

Skin

Serious skin reactions: Use of some NSAIDs, such as Robaxisal C ½, have been associated with rare post-market cases of serious, fatal, or otherwise life-threatening skin reactions, including:

- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued, and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions, or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

Special Populations

Special Risk Groups: Codeine phosphate 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, myxedema, toxic psychosis, prostatic hypertrophy, or urethral stricture.

Pregnant Women
Studies in humans have not been conducted. Robaxisal C ½ crosses the placental barrier and is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Robaxisal C ½ is contraindicated during pregnancy because the codeine component of Robaxisal C ½ significantly increases the rate of malformations if used in the first trimester of pregnancy (deformities of the respiratory tract, slight increase in cleft lip and palate). In the last trimester of pregnancy, codeine may cause withdrawal symptoms in the neonate (also in the foetus if therapy is discontinued before birth).

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** and **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.

Due to the NSAID component in Robaxisal C ½, during the third trimester of pregnancy there are also risks of premature closure of the ductus arteriosus and the potential to prolong parturition. During the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) there is risk of possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and post marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment, or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID Robaxisal C ½ treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if Robaxisal C ½ treatment extends beyond 48 hours and that NSAIDs Robaxisal C ½ treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis period.

Labour, Delivery and Nursing Women

Since opioids can cross the placental barrier and are excreted in breast milk, Robaxisal C ½ 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 Robaxisal C ½ is used in this population.

Ingestion of ASA prior to delivery may prolong delivery or lead to bleeding in the mother or neonate.

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** 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, Robaxisal C ½ is contraindicated in breast-feeding. Health Practitioners 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 Robaxisal C ½) 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 CLINICAL USE** and **DOSAGE AND ADMINISTRATION**). The safety and efficacy of Robaxisal C ½ have not been studied in the pediatric population. Therefore, use of Robaxisal C ½ is not recommended in patients under 18 years of age.

Use of ASA may be associated with the development of Reye's syndrome in children and teenagers with acute febrile illnesses, especially influenza and varicella. Although a direct causal relationship has not been established, salicylates should not be administered to, or used

by, children or teenagers who have chicken pox or manifest flu symptoms before a physician or pharmacist is consulted about Reye's syndrome, a rare and serious illness.

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**).

Patients with Hepatic and/or Renal Impairment:
Robaxisal C ½ should be given with caution in certain patients such as the debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of Robaxisal C ½ tablets are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

The most frequently observed adverse effects of Robaxisal C ½ are:

Methocarbamol:
The most common complaints to methocarbamol are drowsiness, nausea and dizziness or lightheadedness (seen in approximately 4 to 5 % of patients). The following reactions have been associated with the drug, some of them rarely; in some instances, causal relationships have not been established: headache, nasal congestion, blurred vision, rash, pruritus and urticaria.

ASA:
Gastrointestinal
Ulcer, hemorrhage, dyspepsia, heartburn, epigastric distress, nausea, vomiting, diarrhea, abdominal pain may occur with increasing incidence at higher dosages.

Hepatic
Reversible hepatotoxicity particularly in patients with juvenile rheumatoid arthritis and systemic lupus erythematosus has been reported rarely.

Otic
Tinnitus and hearing loss, usually completely reversible, may occur in patients receiving large doses of ASA or with long-term use and are dose related.

Skin
Skin eruptions and lesions have been reported. Stevens-Johnson's syndrome and DRESS has rarely been associated with ASA.

Chronic salicylate intoxication may result from high doses or from prolonged therapy with high doses. Tinnitus and hearing loss are the most frequent signs of chronic intoxication. Other manifestations such as dimness of vision, headache, dizziness, mental confusion, drowsiness, sweating, thirst, hyperventilation, tachycardia, nausea, vomiting and sometimes diarrhea may occur.

Codeine:
Drug Abuse and Dependence: Codeine can produce drug dependence of the morphine type, and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications.

Sedation
Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced, and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia, and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Post-marketing Experience

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: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, gabapentinoids such as gabapentin and pregabalin, baclofen, 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. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)** and **Psychomotor Impairment**). Robaxisal C ½ should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Methocarbamol may cause color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics, or other CNS depressants concomitantly with Robaxisal C ½ may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with codeine preparations may increase the effect of either the antidepressant or codeine. The concurrent use of anticholinergics with codeine may produce paralytic ileus.

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

Robaxisal C ½ should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

Robaxisal C ½ must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Robaxisal C ½ can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

For acute pain, it is recommended that Robaxisal C ½ be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

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 Robaxisal C ½ is 8 caplets, which is 260 mg codeine (40 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing Robaxisal C ½, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Robaxisal C ½ (see DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Dosing Considerations

Robaxisal C ½ should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

Robaxisal C ½ is not indicated for rectal administration.

Robaxisal C ½ may be taken with or without food, with a glass of water.

Recommended Dose and Dosage Adjustment

Adults:
Regardless of clinical setting, codeine (including Robaxisal C ½) 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 CLINICAL USE**)

Codeine, including Robaxisal C ½, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 6 to 8 hours and not on scheduled intervals.

Adults
Do not exceed 8 caplets in 24 hours.

Patients with Hepatic and / or Renal Impairment:
In patients with any degree of hepatic or renal impairment, the dose initiation should follow a conservative approach.

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. Robaxisal C ½ should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Robaxisal C ½. 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.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal
Robaxisal C ½ should be kept in a safe place, out of the sight and reach of children before, during and after use. Robaxisal C ½ should not be used in front of children since they may copy these actions.

Robaxisal C ½ should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Robaxisal C ½ 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.

Missed Dose
If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

OVERDOSAGE

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

Symptoms: Signs or symptoms of overdose include increased sweating, nausea, vomiting, stomach pain, blurred vision, and loss of appetite.

Signs and symptoms of codeine overdose include miosis (pinpoint pupils), sedation, hypotension, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, respiratory depression, and death. Nausea and vomiting may be observed. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

Treatment: In case of accidental overdose, contact a physician or poison control centre immediately, even if you do not notice any possible signs or symptoms.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics
Central Nervous System:
Codeine phosphate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Codeine phosphate depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Codeine phosphate causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of codeine phosphate overdose.

Gastrointestinal Tract and Other Smooth Muscle:
Codeine phosphate causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary, and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:

Codeine phosphate may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

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.

Immune System:
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Special Populations and Conditions
Pediatrics: Individuals under 12 years of age should not take Robaxisal C ½ tablets.

Geriatrics
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 **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Hepatic Impairment:
Robaxisal C ½ should be prescribed with caution in patients with severe impairment of hepatic function.

Renal Impairment:
Robaxisal C ½ should be prescribed with caution in patients with severe impairment of renal function.

STORAGE AND STABILITY

Robaxisal C ½ should be stored at room temperature (15-30°C).

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:
Each coral and white caplet, coral layer monogrammed "RO", contains methocarbamol 400 mg, ASA 325 mg and codeine phosphate 32.4 mg.

Nonmedicinal ingredients: cellulose, cornstarch, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, magnesium stearate, polyethylene glycol, povidone, sodium starch glycolate and stearic acid.

Packaging:
Robaxisal C ½ is available in packages of 24 & 250.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:
Methocarbamol, codeine phosphate and acetylsalicylic acid (ASA)

Chemical name:
Methocarbamol:

Chemical name:

IUPAC Name: (*RS*)-2-hydroxy-3-(2-methoxyphenoxy)propyl carbamate

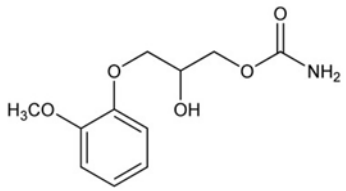
CAS Name: 3-(2-Methoxyphenoxy)-1,2-propanediol 1-carbamate

Additional Names: 3-(*o*-methoxyphenoxy)-2-hydroxypropyl 1-carbamate; 2-hydroxy-3-(*o*-methoxyphenoxy)propyl 1-carbamate; guaiacol glyceryl ether carbamate

Molecular Formula: $C_{11}H_{15}NO_5$

Molecular Weight: 241.24

Structural Formula:



Physiochemical Properties:
Crystals from benzene, melting point 92-94 °C. uv max (water): 222, 274 nm ($E^{1\%}_{1cm}$ 298, 94). 1og P −0.06. Solubility in water at 20°: 2.5 g/100 ml. Soluble in alcohol with heating, propylene glycol; sparingly soluble in chloroform. Insoluble in *n*-hexane, benzene.

Codeine:

Chemical name:

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

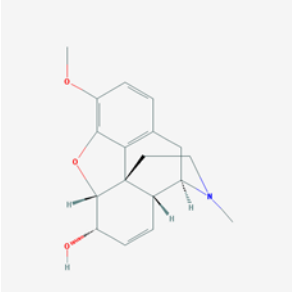
CAS Name: (5α,6α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol

Additional Names: methylmorphine; morphine monomethyl ether; morphine 3-methyl ether

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

Molecular Weight: 299.37

Structural Formula:



Acetylsalicylic Acid (ASA):

Chemical name:

IUPAC Name: 2-(acetyloxy)benzoic acid

CAS Name: 2-(acetyloxy)benzoic acid

Additional Names: acetylsalicylic acid; 2-acetoxybenzoic acid; *o*-acetyloxybenzoic acid; salicylic acid acetate

Molecular formula and molecular mass:

Methocarbamol:

Molecular Formula and molecular mass:

Molecular Formula: $C_{11}H_{15}NO_5$

Molecular Weight: 241.24

Codeine:

Molecular Formula and molecular mass:

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

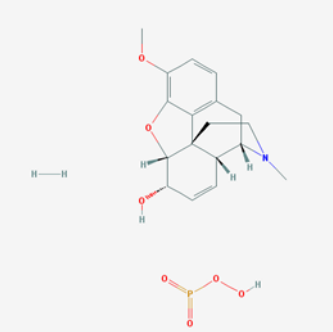
Molecular Weight: 299.37

Codeine derivative: Phosphate

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

Molecular Weight: 397.36

Structural Formula:



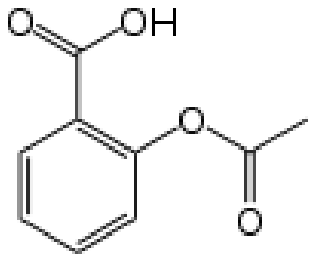
Physiochemical Properties: Fine, white, needle-shaped crystals or crystalline powder. Odorless; affected by light. Solutions acidic to litmus. Freely soluble in water; very soluble in hot water; slightly soluble in alcohol; more soluble in boiling alcohol.

Acetylsalicylic Acid (ASA):

Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16

Structural formula:



Physiochemical Properties: White monoclinic tablets or needle-like crystals. *d* 1.40. Melting point 143 °C; an unstable polymorph shows an endothermic transition at 135 °C. Abs max (0.1 N H_2SO_4): 229 nm ($E^{1\%}_{1cm}$ 484); ($CHCl_3$): 277 nm ($E^{1\%}_{1cm}$ 68). Odorless. Hydrolyzed in moist air to salicylic acid and acetic acid; stable in dry air. Decomposed by boiling water or in solutions of alkali hydroxides and carbonates. pK_a (25 °C) 3.49. One gram dissolves in 300 ml water at 25 °C, in 100 ml water at 37 °C, in 5 ml alcohol, 17 ml chloroform, 10–15 ml ether. Less soluble in anhydrous ether. Inorganic salts are soluble in water, but are decomposed quickly. LD50 orally in mice, rats: 1100, 1500 mg/kg.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{N}Robaxisal C ½

methocarbamol, codeine phosphate and acetylsalicylic acid (ASA)

Read this carefully before you start taking Robaxisal C ½ 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 Robaxisal C ½.

SERIOUS WARNINGS AND PRECAUTIONS

- **Even if you take Robaxisal C ½ as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your healthcare professional.**
- **When you take Robaxisal C ½ it must be swallowed whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking Robaxisal C ½. 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 Robaxisal C ½. They could die from taking it. If a person has not been prescribed Robaxisal C ½, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **DO NOT take Robaxisal C ½ if you are pregnant. Medicines like Robaxisal C ½ may cause harm to you and your baby. If your doctor feels it is necessary for you to take Robaxisal C ½ during pregnancy, your doctor will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe Robaxisal C ½ during this time.**
- **If you took Robaxisal C ½ 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 Robaxisal C ½ 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 Robaxisal C ½ used for?
Robaxisal C ½ is indicated for moderate pain due to or associated with skeletal muscle spasm: acute torticollis, acute strains and sprains, acute low back pain, acute tenosynovitis, ankle sprain, fracture, trauma, acute bursitis, acute myositis, whiplash injury.

How does Robaxisal C ½ work?
Robaxisal C ½ consists of codeine, acetylsalicylic acid (ASA), and methocarbamol.

Codeine is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain. ASA reduces pain, fever and inflammation. Methocarbamol is a muscle relaxant.

What are the ingredients in Robaxisal C ½?
Medicinal ingredients: methocarbamol, acetylsalicylic acid (ASA) and codeine phosphate
Non-medicinal ingredients: Cellulose, cornstarch, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, magnesium stearate, polyethylene glycol, povidone, sodium starch glycolate and stearic acid.

Robaxisal C ½ comes in the following dosage forms:
Tablet, each of which contains methocarbamol 400 mg, ASA 325 mg and codeine phosphate 32.4 mg

Do not use Robaxisal C ½ if:
- your doctor did not prescribe it for you
- you are allergic to methocarbamol, ASA, codeine phosphate or any of the other ingredients in Robaxisal C ½
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- 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
- have a blood clotting disorder (such as hemophilia, von Willebrand's disease, thrombocytopenia, or severe vitamin K deficiency)
- you have had an allergic reaction (such as problems breathing, itchiness, rash, swelling) to ASA or other nonsteroidal anti-inflammatory drugs (NSAIDs) or to tartrazine dye.

- you have stomach ulcers or other serious stomach or bowel sores.
- you have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose.
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take Robaxisal C ½, 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 Robaxisal C ½.
- **Children, teenagers, and young adults with varicella or influenza, unless directed by a physician.**

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Robaxisal C ½. 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
- are taking tranquilizers, sedatives, sedating antihistamines, other depressants, other salicylates, or 3 or more alcoholic beverages per day
- have a history of sleep apnea
- have asthma associated nasal polyps, as this means an increased risk of sensitivity to ASA
- have a history of bleeding or are taking blood thinners
- suffer from migraines
- are pregnant, planning on becoming or become pregnant while taking Robaxisal C ½.

Other warnings you should know about:
Robaxisal C ½ 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

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.

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 questions or

concerns about abuse, addiction, or physical dependence.

Reye's syndrome: ASA may increase the risk of Reye's syndrome, a rare but often fatal condition. Caution should be used in administering ASA-containing medications to young adults who have fever, flu, or chicken pox. Robaxisal C ½ should not be administered to children.

Do not take this medicine for 5 to 7 days before any surgery, including dental surgery, unless otherwise directed by your physician or dentist.

Medical tests: Before you have any medical tests done, tell the person in charge that you are taking Robaxisal C ½. ASA and codeine may interfere with the results of certain tests done in blood and urine.

Testing and check-ups: Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse.
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping).
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing).

Pregnancy, nursing, labour and delivery: Do not use Robaxisal C ½ while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. Robaxisal C ½ can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines: Before you do tasks, which may require special attention, you should wait until you know how you react to Robaxisal C ½. Robaxisal C ½ 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 Robaxisal C ½.

Serotonin toxicity (also known as serotonin syndrome): Codeine, one of the ingredients of Robaxisal C ½ can cause serotonin toxicity (also known as 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 toxicity (also known as serotonin syndrome) if you take Robaxisal C ½ with certain antidepressants or migraine medications.

Serotonin toxicity (also known as 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.

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.

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.

Serious Skin Reactions: In rare cases, serious or life-threatening skin reactions listed below have been reported with some NSAIDs, such as Robaxisal C ½.

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS),
- toxic epidermal necrolysis (TEN),
- exfoliative dermatitis and
- erythema multiforme

You may be at a greater risk of experiencing a serious skin reaction usually during the first month of treatment. See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Worsened Pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia), even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your doctor if you notice a change like this in your pain while you are taking Robaxisal C ½.

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 Robaxisal C ½:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Robaxisal C ½. 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 Robaxisal C ½.
- other 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 Robaxisal C ½ with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- antiepileptics (medicines used to prevent and control seizures e.g., gabapentinoids such as gabapentin and pregabalin).
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- tranquilizers, sedatives, sedating antihistamines, other depressants, other salicylates
- some heart medications (such as beta blockers)
- drugs used to treat migraines (eg. triptans)
- warfarin (such as Coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- St. John's Wort

How to take Robaxisal C ½:
Robaxisal C ½ should not be used in children less than 12 years old.

Codeine, including Robaxisal C ½, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 6 to 8 hours and not on scheduled intervals.

Adults
1 or 2 caplets every 6-8 hours. Do not exceed 8 caplets in 24 hours.

Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:
Your dose is personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Robaxisal C ½ for up to 7 days. If you need to take Robaxisal C ½ 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.

Review your pain regularly with your doctor to determine if you still need Robaxisal C ½. Be sure to use Robaxisal C ½ only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Robaxisal C ½, tell your doctor immediately.

Stopping your Medication
If you have been taking Robaxisal C ½ 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 Robaxisal C ½. 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 treatments 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 Robaxisal C ½.

Refilling your Prescription for Robaxisal C ½:
A new written prescription is required from your doctor each time you need more Robaxisal C ½. 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 pain management.

Overdose:

If you think you have taken too much Robaxisal C ½, 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
- pinpoint pupils
- nausea and vomiting
- low blood pressure

Missed Dose:
If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using Robaxisal C ½?
These are not all the possible side effects you may feel when taking Robaxisal C ½. 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

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Robaxisal C ½.

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	
Uncommon			
Reye's syndrome: rash on the palms of hands and feet, severe vomiting, high fever, weakness, confusions, headache, fast breathing leading to unresponsiveness and death			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Stomach ulcer: heartburn, long lasting stomach pain, loss of appetite and weight loss		✓	
Prolonged bleeding time	✓		
Serotonin toxicity (also known as serotonin syndrome): agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓
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.			✓
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.	✓		

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	
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of the face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			✓
Unknown			
Sleep Apnea: breathing stops for short periods during sleep		✓	

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 Robaxisal C ½ in a secure place to prevent theft, misuse, or accidental exposure.
- Store at room temperature (15-30°C).
- Keep Robaxisal C ½ 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 Robaxisal C ½, get emergency help right away.

Disposal:
Robaxisal C ½ 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 Robaxisal C ½:

- 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://health-products.canada.ca/dpd-bdpp/), or by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC, Mississauga, Ontario L5R 4B2, or by calling 1-888-275-9938.

This leaflet was prepared by GlaxoSmithKline Consumer Healthcare ULC

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