HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CODEINE SULFATE ORAL SOLUTION safely and effectively. See full prescribing information for CODEINE SULFATE ORAL SOLUTION.

CODEINE SULFATE ORAL SOLUTION CII
Initial U.S. Approval: 1950

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

---------- INDICATIONS AND USAGE ----------

Codeine sulfate is an opioid analgesic indicated for the management of mild to moderately severe pain where the use of an opioid analgesic is appropriate. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Usual adult dosage: 15 to 60 mg (2.5 mL to 10 mL) up to every 4 hours as needed. (2.2)

Doses above 60 mg may fail to give commensurate pain relief, and may be associated with an increased incidence of undesirable side effects. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Oral Solution: Each 5 mL contains 30 mg of codeine sulfate. (3)

---------- CONTRAINDICATIONS ----------

- Postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy (4)
- Hypersensitivity to codeine or any component of the product (4)
- Respiratory depression in the absence of resuscitative equipment (4)
- Acute or severe bronchial asthma or hypercarbia (4)
- Paralytic Ileus (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of death in ultra-rapid metabolizers: Conversion of codeine into its active metabolite, morphine, may occur more rapidly and completely resulting in higher than expected morphine levels and respiratory depression or death. (5.1)
- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.2)
- Controlled substance: Codeine sulfate is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.3)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Elevation of intracranial pressure: May be markedly exaggerated in the presence of head injury, other intracranial lesions. (5.5)
- Hypotensive effect: Increased risk with compromised ability to maintain blood pressure. (5.6)
- Prolonged gastric obstruction: Do not administer codeine sulfate to patients with gastrointestinal obstruction, especially paralytic ileus. (5.7)
- Pancreatic/biliary tract disease: May cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions. (5.8)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.10)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions include: drowsiness, light-headedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating, and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Roxane Laboratories, Inc. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

- CNS depressants: Increased risk of additive CNS depression. Use with caution in reduced dosages. (7.1)
- Anticholinergics: Additive risk of urinary retention and paralytic ileus. (7.3)
- Antidepressants: May cause excessive sedation, acute hypotension and excessive anticholinergic effects. Codeine sulfate should not be used in patients taking MAOIs or within 14 days of stopping such treatment. (7.4)
- CYP2D6 inhibitors and CYP3A4 inhibitors and inducers: Concomitant use of cytochrome P450 2D6 and 3A4 enzyme inducers or inhibitors may result in an altered response to codeine. Monitor analgesic activity and adverse drug reactions. (7.5)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. (8.3)
- Pediatric use: Codeine is contraindicated for postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy (8.4)
- Geriatric patients (8.5), Renal impairment (8.6), Hepatic impairment (8.7): Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Individualization of Dosage
2.2 Initiation of Therapy
2.3 Cessation of Therapy
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Death Related to Ultra-Rapid Metabolism of Codeine to Morphine
5.2 Respiratory Depression
5.3 Misuse and Abuse of Opioids
5.4 Interaction with Alcohol and Drugs of Abuse
5.5 Head Injury and Increased Intracranial Pressure
5.6 Hypotensive Effect
5.7 Gastrointestinal Effects
5.8 Use in Pancreatic/Biliary Tract Disease
5.9 Special Risk Patients
5.10 Driving and Operating Machinery
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
7.1 Central Nervous System (CNS) Depressants
7.2 Mixed Agonist/Antagonist Opioid Analgesics
7.3 Anticholinergics
7.4 Antidepressants
7.5 CYP2D6 and CYP3A4 Inhibitors and Inducers
7.6 Drug-Laboratory Test Interaction
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Symptoms
10.2 Treatment
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.3 Reproduction and Developmental Toxicology
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Information for Patients and Caregivers

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

1 INDICATIONS AND USAGE

Codeine sulfate is an opioid analgesic indicated for the management of mild to moderately severe pain where the use of an opioid analgesic is appropriate.

2 DOSAGE AND ADMINISTRATION

Selection of patients for treatment with codeine sulfate should be governed by the same principles that apply to the use of similar opioid analgesics. Individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

2.1 Individualization of Dosage

As with any opioid drug product, adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of codeine sulfate, attention should be given to the following:

- the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
- the reliability of the relative potency estimate used to calculate the equivalent codeine sulfate dose needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medications;
- the type and severity of the patient's pain;
- risk factors for abuse or addiction, including a prior history of abuse and addiction.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

Continual re-evaluation of the patient receiving codeine sulfate is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. During chronic therapy, especially for noncancer-related pain, the continued need for the use of opioid analgesics should be re-assessed as appropriate.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between the physician, other members of the healthcare team, the patient, and the caregiver/family.

2.2 Initiation of Therapy

The usual adult dosage is 15 mg to 60 mg (2.5 mL to 10 mL) repeated up to every four hours as needed for pain. The maximum 24 hour dose is 360 mg.

Titrate the dose based upon the individual patient's response to their initial dose of codeine. Adjust the dose to an acceptable level of analgesia taking into account the improvement in pain intensity and the tolerability of the codeine by the patient.

It should be kept in mind, however, that tolerance to codeine sulfate can develop with continued use and that the incidence of untoward effects is dose-related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain and are associated with an appreciably increased incidence of undesirable side effects.

2.3 Cessation of Therapy

When the patient no longer requires therapy with codeine sulfate, gradually taper the dose to prevent signs and symptoms of withdrawal in the physically dependent patient.

3 DOSAGE FORMS AND STRENGTHS

Each 5 mL of clear, reddish-orange to orange codeine sulfate oral solution contains codeine sulfate, USP 30 mg. The concentration of the 30 mg per 5 mL solution is 6 mg/mL.

4 CONTRAINDICATIONS

Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.1)]*.

Codeine sulfate is contraindicated in patients with known hypersensitivity to codeine or any components of the product. Persons known to be hypersensitive to certain other opioids may exhibit cross-sensitivity to codeine.

Codeine sulfate is contraindicated in patients with respiratory depression in the absence of resuscitative equipment *[see Warnings and Precautions (5.2)]*.

Codeine sulfate is contraindicated in patients with acute or severe bronchial asthma or hypercarbia.

Codeine sulfate is contraindicated in any patient who has or is suspected of having paralytic ileus.

5 WARNINGS AND PRECAUTIONS

5.1 Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine in the post-operative 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). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine *[see Use in Specific Populations (8.3)]*.

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). 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. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) *[see Overdosage (10.1)]*.

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 is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

When prescribing codeine, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose *[see Use in Specific Populations (8), Overdosage (10.1)].*

5.2 Respiratory Depression

Respiratory depression is the primary risk of codeine sulfate. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. Codeine produces dose-related respiratory depression.

Caution should be exercised when codeine sulfate is used postoperatively, in patients with pulmonary disease or shortness of breath, or whenever ventilatory function is depressed. Use opioids, including codeine sulfate, with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of codeine sulfate may increase airway resistance and decrease respiratory drive to the point of apnea. Consider alternative non-opioid analgesics and use codeine sulfate only under careful medical supervision at the lowest effective dose in such patients *[see Overdosage (10)].*

5.3 Misuse and Abuse of Opioids

Codeine sulfate is an opioid agonist of the morphine-type and a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.

Patients should be assessed for their risk for opioid abuse or addiction prior to being prescribed opioids

Codeine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing codeine sulfate in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Codeine may be abused by crushing, chewing, snorting or injecting the product. Misuse and abuse of codeine sulfate poses a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9.2)]*.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

5.4 Interaction with Alcohol and Drugs of Abuse

Codeine sulfate may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, because respiratory depression, hypotension, profound sedation, coma or death may result.

5.5 Head Injury and Increased Intracranial Pressure

Respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure resulting from vasodilation following CO_2 retention may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids including codeine sulfate, can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

5.6 Hypotensive Effect

Codeine sulfate may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs such as phenothiazines or general anesthetics. Codeine sulfate may produce orthostatic hypotension and syncope in ambulatory patients.

Administer codeine sulfate with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.7 Gastrointestinal Effects

Do not administer codeine sulfate to patients with gastrointestinal obstruction, especially paralytic ileus because codeine sulfate diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.

Chronic use of opioids, including codeine sulfate, may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder. Codeine sulfate may cause or aggravate constipation.

The administration of codeine sulfate may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.8 Use in Pancreatic/Biliary Tract Disease

Use codeine sulfate with caution in patients with biliary tract disease, including acute pancreatitis, as codeine sulfate may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

5.9 Special Risk Patients

Use codeine sulfate with caution in patients with severe renal or hepatic impairment, hypothyrodism, Addison's disease, prostatic hypertrophy, or urethral stricture and in elderly or debilitated patients *[see Use in Specific Populations (8.5)]*. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Extreme caution should be exercised in the administration of codeine sulfate to patients with CNS depression, acute alcoholism, and delirium tremens.

All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Keep Codeine Sulfate Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

5.10 Driving and Operating Machinery

Caution patients that codeine sulfate could impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

Caution patients about the potential combined effects of codeine sulfate with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics, and alcohol *[see Drug Interactions (7.1)]*.

6 ADVERSE REACTIONS

Serious adverse reactions associated with codeine are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

The most frequently observed adverse reactions with codeine administration include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, sweating, and constipation.

Other adverse reactions include allergic reactions, euphoria, dysphoria, abdominal pain, and pruritis.

Other less frequently observed adverse reactions expected from opioid analgesics, including codeine sulfate, include:

Cardiovascular system: faintness, flushing, hypotension, palpitations, syncope

Digestive System: abdominal cramps, anorexia, diarrhea, dry mouth, gastrointestinal distress, pancreatitis

Nervous system: anxiety, drowsiness, fatigue, headache, insomnia, nervousness, shakiness, somnolence, vertigo, visual disturbances, weakness

Skin and Appendages: rash, sweating, urticaria

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS) Depressants

Concurrent use of other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol) concomitantly with codeine sulfate may result in additive CNS depression, respiratory depression, hypotension, profound sedation, or coma. Use codeine sulfate with caution and in reduced dosages in patients taking these agents.

7.2 Mixed Agonist/Antagonist Opioid Analgesics

Do not administer mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as codeine sulfate. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

7.3 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

7.4 Antidepressants

Use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants with codeine sulfate may increase the effect of either the antidepressant or codeine. MAOIs markedly potentiate the action of morphine, the major metabolite of codeine. Codeine should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

7.5 CYP2D6 and CYP3A4 Inhibitors and Inducers

Codeine is metabolized by the cytochrome P450 2D6 and 3A4 isoenzymes *[see Clinical Pharmacology (12.3)]*. Patients taking CYP2D6 inhibitors or CYP3A4 inhibitors or inducers may demonstrate an altered response to codeine, therefore analgesic activity should be monitored.

Inhibitors of CYP2D6 or CYP3A4: Since the CYP2D6 and CYP3A4 isoenzymes play a major role in the metabolism of codeine, drugs that inhibit CYP3A4 (e.g., macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)), or CYP2D6 activity (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), may cause decreased clearance of codeine which could lead to an increase in codeine plasma concentrations. If coadministration with codeine sulfate oral solution is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these

patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4: CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of codeine and, therefore, may cause increased clearance of the drug which could lead to a decrease in codeine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to codeine. If co-administration with codeine sulfate oral solution is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

7.6 Drug-Laboratory Test Interaction

Codeine may cause an elevation of plasma amylase and lipase due to the potential of codeine to produce spasm of the sphincter of Oddi. Determination of these enzyme levels may be unreliable for some time after an opiate agonist has been given.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Codeine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Codeine has been shown to have embryolethal and fetotoxic effects (reduced fetal body weights and delayed or incomplete ossification) in the hamster, rat and mouse models at approximately 2 to 4 times the maximum recommended human dose of 360 mg/day based on a body surface area comparison. Maternally toxic doses that were approximately 7 times the maximum recommended human dose of 360 mg/day, were associated with evidence of resorptions and incomplete ossification, including meningioencephalocele and cranioschisis. In contrast, codeine did not demonstrate evidence of embryotoxicity or fetotoxicity in the rabbit model at doses up to 2 times the maximum recommended human dose of 360 mg/day based on a body surface area comparison *[see Nonclincal Pharmacology (13.3)]*.

Nonteratogenic Effects

Neonatal codeine withdrawal has occurred in infants born to addicted and non-addicted mothers who had been taking codeine-containing medications in the days prior to delivery. Typical symptoms of narcotic withdrawal include irritability, excessive crying, tremors, hyperreflexia, seizures, fever, vomiting, diarrhea, and poor feeding. These signs occur shortly after birth and may require specific treatment.

Codeine (30 mg/kg) administered subcutaneously to pregnant rats during pregnancy and for 25 days after delivery increased neonatal mortality at birth. This dose is 0.8 times the maximum recommended human dose of 360 mg/day on a body surface area comparison.

8.2 Labor and Delivery

Opioid analgesics cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Codeine is not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics

may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone, available for reversal of opioid-induced respiratory depression in the neonate.

8.3 Nursing Mothers

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 metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breast-feeding *[see Warnings and Precautions (5.9)]*.

8.4 Pediatric Use

The safety, effectiveness and the pharmacokinetics of codeine sulfate in pediatric patients below the age of 18 have not been established.

Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative 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). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

8.5 Geriatric Use

Codeine may cause confusion and over-sedation in the elderly (aged 65 and older). In general, use caution when selecting a dose for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Start these patients cautiously with lower doses of codeine sulfate or with longer dosing intervals and titrate slowly while carefully monitoring for side effects.

8.7 Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of codeine in this patient population are unknown. Start these patients cautiously with lower doses of codeine sulfate or with longer dosing intervals and titrate slowly while carefully monitoring for side effects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Codeine sulfate is an opioid agonist and is a Schedule II controlled substance. Codeine sulfate can be abused and is subject to criminal diversion.

9.2 Abuse

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Healthcare provider shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

The risks of misuse and abuse should be considered when prescribing or dispensing codeine sulfate. Concerns about abuse and addiction, should not prevent the proper management of pain, however, treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. The converse is also true. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Codeine is intended for oral use only. Abuse of codeine poses a risk of overdose and death. The risk is increased with concurrent abuse of alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.2), Overdosage (10.1)]*.

9.3 Dependence

Tolerance to opioids is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). Physical dependence is manifested by withdrawal symptoms

after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are frequent during chronic opioid therapy.

Instruct patients using codeine sulfate not to change their dose without first contacting their health care providers. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued *[see Dosage and Administration (2.3)]*.

10 OVERDOSAGE

10.1 Symptoms

Acute overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

Codeine may cause 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 overdose situations.

10.2 Treatment

Give primary attention to re-establishment of a patent airway and institution of assisted or controlled ventilation. Employ supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Induction of emesis is not recommended because of the potential for CNS depression and seizures. Activated charcoal is recommended if the patient is awake and able to protect his/her airway. In persons who are at risk for abrupt onset of seizures or mental status depression, activated charcoal should be administered by medical or paramedical personnel capable of airway management to prevent aspiration in the event of spontaneous emesis. Severe agitation or seizures should be treated with an intravenous benzodiazepine.

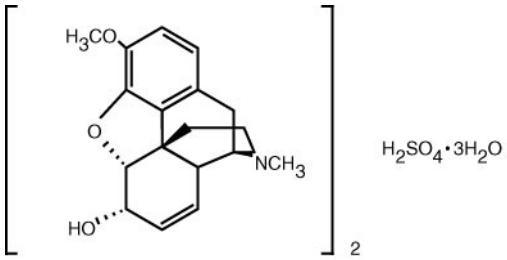
The pure opioid antagonist, naloxone, is a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of codeine sulfate, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed by the label of the product.

Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to codeine sulfate overdose. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. Reserve use of an opioid antagonist for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, initiate administration of the antagonist with care and titrate with smaller than usual doses.

11 DESCRIPTION

Chemically, codeine sulfate is morphinan-6-ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-(5α,6α)-, sulfate (2:1) (salt), trihydrate. Codeine sulfate trihydrate is a fine, white, crystalline powder which is soluble in water and insoluble in chloroform and ether. Its empirical formula is $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$ and its molecular weight is 750.85 g/mol.

Its structure is as follows:



Each 5 mL of oral solution contains 30 mg of codeine sulfate, USP and the following inactive ingredients: ascorbic acid, citric acid, disodium edetate, FD&C Red No. 40, FD&C Yellow No. 6, glycerin, Orange Flavor XBF-709818 (artificial flavors, propylene glycol), sodium benzoate, sorbitol, sucralose, and water. The pH of the oral solution is 3.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Codeine is an opioid agonist, related to morphine, but with less potent analgesic properties. Codeine is selective for the mu receptor, but with a much weaker affinity than morphine. The analgesic properties of codeine have been speculated to come from its conversion to morphine, although the exact mechanism of analgesic action remains unknown.

Effects of the Central Nervous System (CNS): The principal therapeutic action of codeine is analgesia. Although the precise mechanism of the analgesic action is unknown, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. Other CNS effects of codeine include anxiolysis, euphoria, and feelings of relaxation. Codeine causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Codeine and other related opioids depress the cough reflex by direct effect on the cough center in the medulla. Codeine may also cause miosis.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle: Gastric, biliary and pancreatic secretions may be decreased by codeine. Codeine also causes a reduction in motility and is associated with an increase in 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 is increased to the point of spasm. The end result may be constipation. Codeine can cause a marked increase in biliary tract pressure as a result of the spasm of the sphincter of Oddi. Codeine may also cause spasms of the sphincter of the urinary bladder.

Effects on the Cardiovascular System: In therapeutic doses, codeine does not usually exert major effects on the cardiovascular system. Codeine produces peripheral vasodilation which may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

Endocrine System: Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth

hormone (GH) secretion, and pancreatic secretion of insulin and glucagons in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System: Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

12.2 Pharmacodynamics

Codeine plasma concentrations do not correlate with codeine brain concentrations or relief of pain.

The minimum effective concentration varies widely and is influenced by a variety of factors, including the extent of previous opioid use, age and general medical condition. Effective doses in tolerant patients may be significantly higher than in opioid-naïve patients.

12.3 Pharmacokinetics

Absorption: Codeine, when administered as codeine sulfate, is absorbed from the gastrointestinal tract with maximum plasma concentration occurring 60 minutes post administration.

Food Effects: When 60 mg codeine sulfate was administered 30 minutes after ingesting a high fat/high calorie meal, there was no significant change in the rate and extent of absorption of codeine.

Steady-state: Administration of 15 mg codeine sulfate every four hours for 5 days resulted in steady-state concentrations of codeine, morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) within 48 hours.

Distribution: Codeine has been reported to have an apparent volume of distribution of approximately 3-6 L/kg, indicating extensive distribution of the drug into tissues. Codeine has low plasma protein binding with about 7-25% of codeine bound to plasma proteins.

Metabolism: About 70-80% of the administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (C6G, about 60%) and via *O*-demethylation to morphine (about 5-10%) and *N*-demethylation to norcodeine (about 10%) respectively. UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucurodination of codeine to C6G. Cytochrome P450 2D6 is the major enzyme responsible for conversion of codeine to morphine (about 5-10%) and P450 3A4 is the major enzyme mediating conversion of codeine to norcodeine. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Morphine and M6G are known to have analgesic activity in humans. The analgesic activity of C6G in humans is unknown. Norcodeine and M3G are generally not considered to possess analgesic properties.

Elimination: Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. Plasma half-lives of codeine and its metabolites have been reported to be approximately 3 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two year carcinogenicity studies have been conducted in F344/N rats and B6C3F1 mice. There was no evidence of carcinogenicity in male and female rats, respectively, at dietary doses up to 70 and 80 mg/kg/day of codeine (approximately 2 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis) for two years. Similarly there was no evidence of carcinogenicity activity in male and female mice at dietary doses up to 400 mg/kg/day

of codeine (approximately 5 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis) for two years.

Mutagenesis: Codeine was not mutagenic in the *in vitro* bacterial reverse mutation assay or clastogenic in the *in vitro* Chinese hamster ovary cell chromosome aberration assay.

Impairment of Fertility: No animal studies were conducted to evaluate the effect of codeine on male or female fertility.

13.3 Reproduction and Developmental Toxicology

Studies on the reproductive and developmental effects of codeine have been reported in the published literature in hamsters, rats, mice and rabbits.

A study in hamsters administered 150 mg/kg twice daily of codeine (oral; approximately 7 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis) reported the development of cranial malformations (i.e., meningoencephalocele) in several fetuses examined; as well as the observation of increases in the percentage of resorptions per litter examined. Doses of 50 and 150 mg/kg, bid resulted in fetotoxicity as demonstrated by decreased fetal body weight. In an earlier study in hamsters, doses of 73-360 mg/kg level (oral; approximately 2-8 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis), reportedly produced cranioschisis in all of the fetuses examined.

In studies in rats, doses at the 120 mg/kg level (oral; approximately 3 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis), in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation.

In pregnant mice, a single 100 mg/kg dose (subcutaneous; approximately 1.4 times the recommended daily dose of 360 mg/day for adults on a mg/mg^2 basis) reportedly resulted in delayed ossification in the offspring.

No teratogenic effects were observed in rabbits administered up to 30 mg/kg (approximately 2 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m^2 basis) of codeine during organogenesis.

16 HOW SUPPLIED/STORAGE AND HANDLING

Codeine Sulfate Oral Solution

Codeine Sulfate Oral Solution, 30 mg per 5 mL is a clear, reddish-orange to orange solution available in one strength as follows:

30 mg per 5 mL Oral Solution

NDC 0054-0294-63: Bottle of 500 mL, packed in a carton with five oral syringes (5 mL) and one measuring cup (5 mL).

Storage

Store at controlled room temperature, 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (between 59° and 86°F).

Protect from light and moisture.

Dispense in well-closed container as defined in the USP/NF.

All opioids, including codeine sulfate, are liable to diversion and misuse both by the general public and healthcare workers and should be handled accordingly.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

17.1 Information for Patients and Caregivers

- Advise patients that codeine sulfate is a narcotic pain medication and should be taken only as directed.
- Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid codeine metabolizer or not. These higher-than-normal levels of morphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. Codeine is contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine for other reasons to monitor for signs of respiratory depression.
- Advise patients that nursing mothers taking codeine can have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Advise nursing mothers to watch for signs of morphine toxicity in their infants which includes increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's doctor immediately if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911 (or local emergency services).
- Advise patients not to adjust the dose of codeine sulfate without consulting a physician or other healthcare professional.
- Instruct patients on how to measure and take the correct dose of Codeine Sulfate Oral Solution.
- Advise patients that codeine may cause drowsiness, dizziness, or lightheadedness and may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Advise patients started on codeine sulfate or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected.
- Advise patients that codeine sulfate will add to the effects of alcohol and other CNS depressants (such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and monoamine oxidase [MAO] inhibitors).
- Advise patients not to combine codeine sulfate with central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, and not to combine with alcohol because dangerous additive effects may occur, resulting in serious injury or death.
- Advise patients that codeine sulfate is a potential drug of abuse. They must protect it from theft. It should never be given to anyone other than the individual for whom it was prescribed.
- Advise patients to keep codeine sulfate in a secure place out of the reach of children.
- Advise patients of the potential for severe constipation when taking codeine sulfate; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of therapy.
- Advise patients of the most common adverse events that may occur while taking codeine sulfate: drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, constipation, and sweating.
- Advise patients that if they miss one dose of Codeine Sulfate Oral Solution they can take the dose when they remember it if they have pain, or they can wait for the next dose.
- If patients have been receiving treatment with codeine sulfate for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Advise women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiating or continuing therapy with codeine sulfate.

- Advise patients that safe use in pregnancy has not been established and prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.

Manufactured by:
Roxane Laboratories, Inc., Columbus, Ohio 43216

10007857/02

Revised April 2013

MEDICATION GUIDE

CODEINE SULFATE (koh-deen) CII
Oral Solution

IMPORTANT:

- **Do not give CODEINE Sulfate Oral Solution to a child to treat pain after tonsillectomy or adenoidectomy surgery.**
  - **When you take CODEINE Sulfate Oral Solution, some or all of it changes into morphine in your body.**
  - **In some children and adults this happens very quickly, and can cause you to stop breathing and cause death due to an overdose.**
- **Women who breastfeed should talk to their healthcare provider before taking CODEINE Sulfate Oral Solution.**
  - **When you take CODEINE Sulfate Oral Solution, some or all of it changes into morphine in your body.**
  - **In some women, this happens very quickly. Codeine and morphine pass into your breast milk. A large amount of morphine can cause your baby to die.**
- **Call your healthcare provider or get emergency medical help right away if anyone taking CODEINE Sulfate Oral Solution, or your breastfeeding baby has any of the symptoms listed below:**
  - **Increased sleepiness**
  - **Confusion**
  - **Difficulty breathing**
  - **Shallow breathing**
  - **Limpness**
  - **Your baby has difficulty breastfeeding**
- **Keep Codeine Sulfate Oral Solution in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes Codeine Sulfate, get emergency help right away.**

Read the Medication Guide that comes with Codeine Sulfate Oral Solution before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Codeine Sulfate Oral Solution?

- Codeine Sulfate Oral Solution can cause serious side effects, including death.
- Take Codeine Sulfate Oral Solution exactly as prescribed by your healthcare provider. If you take the wrong dose or strength of Codeine Sulfate Oral Solution, you could overdose and die.

- It is especially important when you take Codeine Sulfate Oral Solution that you know exactly what dose and strength to take, and the right way to measure your medicine. Your healthcare provider or pharmacist should show you the right way to measure your medicine.
- Always use the oral syringe provided with Codeine Sulfate Oral Solution, 30 mg per 5 mL (6 mg/mL) to help make sure you measure the right amount.

What is Codeine Sulfate Oral Solution?

- Codeine Sulfate Oral Solution is in a group of drugs called narcotic pain relievers. Codeine Sulfate Oral Solution is only for people who have mild to moderately severe pain.
- Codeine Sulfate Oral Solution is a federally controlled substance (CII) because it is an opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.
- Prevent theft, misuse or abuse. Keep Codeine Sulfate Oral Solution in a safe place to keep it from being stolen. Codeine Sulfate can be a target for people who misuse or abuse prescription medicines or street drugs.
- Never give Codeine Sulfate Oral Solution to anyone else, even if they have the same symptoms you have. It may harm them or even cause death.
- Selling or giving away this medicine is against the law.
- It is not known if Codeine Sulfate Oral Solution is safe and effective in children under age 18 years of age.

Who should not take Codeine Sulfate Oral Solution?

- Do not give Codeine Sulfate Oral Solution to a child to treat pain after tonsillectomy or adenoidectomy surgery.
- Do not take Codeine Sulfate Oral Solution if you:
  - are allergic to Codeine or any of the ingredients in Codeine Sulfate Oral Solution. See the end of this Medication guide for a complete list of ingredients in Codeine Sulfate Oral Solution.
  - are having an asthma attack or have severe asthma, trouble breathing, or lung problems.
  - have a bowel blockage, called paralytic ileus.

What should I tell my healthcare provider before taking Codeine Sulfate?

- Before taking Codeine Sulfate Oral Solution, tell your healthcare provider if you:
  - have trouble breathing or lung problems
  - have had a head injury
  - have liver or kidney problems
  - have been told by your healthcare provider that you are a "rapid metabolizer" of certain medicines
  - have had adrenal gland problems, such as Addison's disease
  - have severe scoliosis that affects your breathing
  - have thyroid problems
  - have problems urinating or enlargement of your prostate
  - have had convulsions or seizures
  - have a past or present drinking problem or alcoholism
  - have severe mental problems
  - have constipation or other bowel problems
  - have problems with your pancreas or gallbladder
  - have past or present substance abuse or drug addiction
  - plan to have surgery
  - have any other medical conditions

- are pregnant or plan to become pregnant. It is not known if Codeine Sulfate Oral Solution will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. If you take Codeine Sulfate Oral Solution right before your baby is born, your newborn could have breathing problems. Your baby may also have withdrawal symptoms because his body has become used to the medicine. Symptoms of withdrawal in a newborn baby may include:
  - irritability
  - vomiting
  - weight loss
  - fever
  - diarrhea or more stools than normal
  - being very active
  - problems sleeping
  - high pitched cry
  - shaking (tremors)

- are breast-feeding or plan to breast-feed
  - See the box with Important information at the top of this Medication Guide.
  - If you stop breast-feeding, your baby may have withdrawal symptoms. See the list of withdrawal symptoms above. If your baby has any of these symptoms you need to contact your healthcare provider right away. If you can not reach your healthcare provider, take your baby to your local hospital emergency room or call your local emergency medical service. You and your healthcare provider should decide if you will take Codeine Sulfate Oral Solution or breast-feed.

- Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes the doses of medicines that you take with Codeine Sulfate Oral Solution may need to be changed if used together. Codeine Sulfate Oral Solution and other medicines may affect each other causing serious side effects. Be especially careful about taking other medicines that make you sleepy such as:
  - sleeping pills
  - anti-depressants
  - other pain medicines
  - anticholinergic medicines
  - anti-nausea medicines
  - antibiotic or antifungal medicines
  - tranquilizers
  - heart medicines
  - antihistamines
  - anti-seizure medicines
  - anti-anxiety medicines
- Do not take Codeine Sulfate Oral Solution if you already take a monoamine oxidase inhibitor medicine (MAOI) or within 14 days after you stop taking an MAOI medicine.
- Do not take any new medicine while using Codeine Sulfate until you have talked with your healthcare provider or pharmacist. They will tell you if it is safe to take other medicines with Codeine Sulfate Oral Solution.
- Ask your healthcare provider if you are not sure if your medicine is one listed above.
- Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Codeine Sulfate Oral Solution?

- See "What is the most important information I should know about Codeine Sulfate Oral Solution?"

- **Take Codeine Sulfate Oral Solution exactly as prescribed.** Do not change your dose unless your healthcare provider tells you to. Your healthcare provider may change your dose after seeing how the medicine affects you. Call your healthcare provider if your pain is not well controlled with your prescribed dose of Codeine Sulfate Oral Solution. **You can take Codeine Sulfate Oral Solution with or without food.**
- **Make sure you understand exactly how to measure your dose.** Always use the oral syringe provided with your Codeine Sulfate Oral Solution, 30 mg per 5 mL (6 mg/mL) to help make sure you measure the right amount. Ask your healthcare provider or pharmacist if you are not sure what dose of Codeine Sulfate Oral Solution you should take or if you are not sure how to use the oral syringe.
- **Do not stop taking Codeine Sulfate Oral Solution suddenly.** If you have been taking Codeine Sulfate Oral Solution for more than a few weeks, stopping Codeine Sulfate Oral Solution suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). If your healthcare provider decides you no longer need Codeine Sulfate Oral Solution, ask how to slowly reduce this medicine. Do not stop taking Codeine Sulfate Oral Solution without talking to your healthcare provider.

  If you take too much Codeine Sulfate Oral Solution, call your healthcare provider or go to the nearest hospital emergency room right away.
- **If you miss one dose of Codeine Sulfate Oral Solution** you can take the dose when you remember it if you have pain, or you can wait for the next dose.
- Talk with your healthcare provider regularly about your pain to see if you still need to take Codeine Sulfate.

What should I avoid while taking Codeine Sulfate Oral Solution?

- You should not drink alcohol while using Codeine Sulfate Oral Solution. Drinking alcohol with Codeine Sulfate Oral Solution may increase your risk of having dangerous side effects or death.
- **Do not drive, operate heavy machinery, or do other dangerous activities,** especially when you start taking Codeine Sulfate Oral Solution and when your dose is changed, until you know how Codeine Sulfate Oral Solution affects you. Codeine Sulfate Oral Solution can make you sleepy. Ask your healthcare provider to tell you when it is okay to do these activities.

What are the possible side effects of Codeine Sulfate Oral Solution?

- **See "What is the most important information I should know about Codeine Sulfate Oral Solution?"**

- Codeine Sulfate Oral Solution can cause serious breathing problems that can become life-threatening, especially if Codeine Sulfate is used the wrong way. Call your healthcare provider or get help right away if:

  - your breathing slows down
  - you have shallow breathing (little chest movement with breathing)
  - you feel faint, dizzy, confused, or
  - you have any other unusual symptoms

These can be symptoms that you have taken too much Codeine Sulfate Oral Solution (overdose) or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- **Codeine Sulfate Oral Solution can cause your blood pressure to drop.** This can make you feel dizzy if you get up fast from sitting or lying down. Low blood pressure is also more likely to happen if you take other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lose blood or take certain other medicines.
- **There is a risk of abuse or addiction with Codeine Sulfate Oral Solution.** The risk is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

- **Codeine Sulfate Oral Solution can cause physical dependence.** Do not stop taking Codeine Sulfate Oral Solution or any other opioid without talking to your healthcare provider about how to slowly stop your medicine. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Tell your healthcare provider if you have any of these symptoms of withdrawal while slowly stopping Codeine Sulfate Oral Solution:
  - feel restless
  - dilated pupils of your eyes
  - tearing eyes
  - feel irritable or anxious
  - runny nose
  - trouble sleeping
  - yawning
  - increase in your blood pressure
  - sweating
  - faster breathing, or faster heart beats
  - chills or hair on your arms "stand up"
  - nausea, loss of appetite, vomiting, diarrhea, stomach-area (abdominal) cramps
  - muscle aches, backache
- Common side effects of Codeine Sulfate Oral Solution include:
  - constipation
  - dizziness
  - nausea
  - drowsiness
  - sleepiness
  - vomiting
  - lightheadedness
  - sweating

- Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines from the opioid class. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking Codeine Sulfate Oral Solution.
- Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
- These are not all the possible side effects of Codeine Sulfate Oral Solution. For more information, ask your healthcare provider or pharmacist.
- Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Codeine Sulfate Oral Solution?

- Store Codeine Sulfate Oral Solution at room temperature, between 59°F to 86°F (15°C to 30°C), away from the light.
- Keep Codeine Sulfate Oral Solution out of the reach of children. Accidental overdose by a child is a medical emergency and can lead to death.

General Information about Codeine Sulfate Oral Solution

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Codeine Sulfate Oral Solution for a condition for which it was not prescribed. Do not give your Codeine Sulfate Oral Solution to other people, even if they have the same symptoms you have. Selling or giving away Codeine Sulfate Oral Solution may harm others, may cause death, and is against the law.
- This Medication Guide summarizes the most important information about Codeine Sulfate Oral Solution. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Codeine Sulfate Oral Solution that is written for healthcare professionals.

- For more information about Codeine Sulfate Oral Solution, go to www.roxane.com or call Roxane Laboratories, Inc. at 1-800-962-8364.

What are the ingredients in Codeine Sulfate Oral Solution?

- Active ingredient: codeine sulfate

Inactive ingredients: ascorbic acid, citric acid, disodium edetate, FD&C Red No.40, FD&C Yellow No.6, glycerin, Orange Flavor XBF-709818 (artificial flavors, propylene glycol), sodium benzoate, sorbitol, sucralose and water.

Instructions for Use
Codeine Sulfate (koh-deen) (CII)
Oral Solution

Oral Syringe

Important information about measuring Codeine Sulfate Oral Solution:

- Always use the oral syringe provided with your Codeine Sulfate Oral Solution to make sure you measure the right amount.
- Measure the dose of medicine from the widest part of the plunger. Do not measure from the narrow tip. See Figure 1**.**

1. Remove the protective storage cap from the syringe.
2. Insert the tip of the oral syringe into the medicine bottle.
3. Pull back the plunger to the line that matches the dose prescribed by your healthcare provider.
4. Remove the oral syringe from the medicine bottle.
5. Take your medicine by slowly pushing the plunger until the oral syringe is empty.
6. Replace the cap and oral syringe in a dry and clean place.

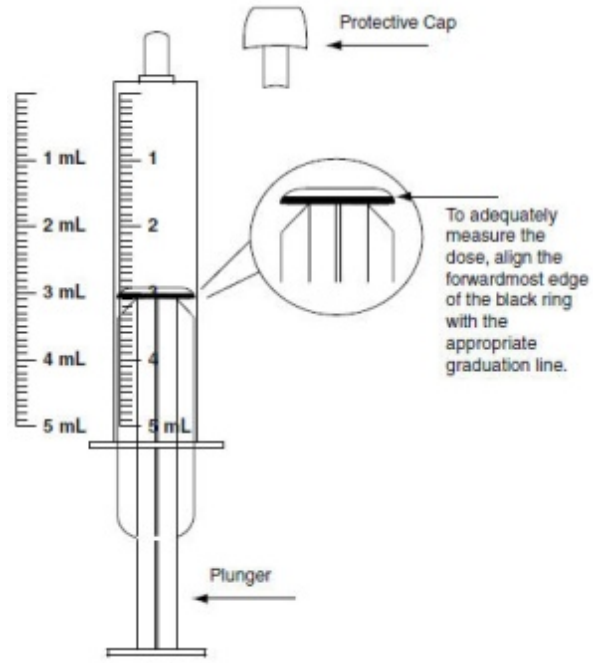


Figure 1

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured by:
Roxane Laboratories, Inc.
Columbus, Ohio 43216

10007857/02

Revised May 2013