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: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **Ensure accuracy when prescribing, dispensing, and administering Codeine Sulfate Oral Solution. Dosing errors due to confusion between mg and mL can result in accidental overdose and death. (2.1, 5.1)**
- **Codeine Sulfate Oral Solution exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)**
- **Accidental ingestion of Codeine Sulfate Oral Solution, especially by children, can result in a fatal overdose of codeine. (5.3)**
- **Prolonged use of Codeine Sulfate Oral Solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **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. (5.5)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Codeine Sulfate Oral Solution requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine (5.6, 7).**
- **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. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation (5.7, 7)**

RECENT MAJOR CHANGES

Boxed Warning	12/2016
Indications and Usage	12/2016
Dosage and Administration	12/2016
Contraindications	12/2016
Warnings and Precautions	12/2016

INDICATIONS AND USAGE

Codeine Sulfate Oral Solution is an opioid agonist, indicated for the management of mild to moderate pain, where treatment with an opioid is appropriate and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Codeine Sulfate Oral Solution for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with 15 to 60 mg (2.5 mL to 10 mL) every 4 hours as needed. (2.2)
- Do not stop Codeine Sulfate Oral Solution abruptly in a physically dependent patient. (2.4)

DOSAGE FORMS AND STRENGTHS

Oral solution: 30 mg/5 mL (6 mg/mL). (3)

CONTRAINDICATIONS

- Significant respiratory depression. (4)
- Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Hypersensitivity to codeine. (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of Codeine Sulfate Oral Solution in patients with circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of Codeine Sulfate Oral Solution in patients with impaired consciousness or coma. (5.12)

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 West-Ward Pharmaceuticals Corp. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue Codeine Sulfate Oral Solution if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Codeine Sulfate Oral Solution because they may reduce analgesic effect of Codeine Sulfate Oral Solution or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: 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. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering Codeine Sulfate Oral Solution. Dosing errors due to confusion between mg and mL, and other codeine solutions of different concentrations can result in accidental overdose and death *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.

Addiction, Abuse, and Misuse

Codeine Sulfate Oral Solution exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Codeine Sulfate Oral Solution, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.2)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Codeine Sulfate Oral Solution. Monitor for respiratory depression, especially during initiation of Codeine Sulfate Oral Solution or following a dose increase *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of Codeine Sulfate Oral Solution, especially by children, can result in a fatal overdose of codeine *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Codeine Sulfate Oral Solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

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 [*see Warnings and Precautions (5.5)*].

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Codeine Sulfate Oral Solution requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine [*see Warnings and Precautions(5.6), Drug Interactions (7)*].

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 (5.7), Drug Interactions (7)*].

- **Reserve concomitant prescribing of Codeine Sulfate Oral Solution 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.**

1 INDICATIONS AND USAGE

Codeine Sulfate Oral Solution is indicated for the management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.2)]*, reserve Codeine Sulfate Oral Solution for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Ensure accuracy when prescribing, dispensing, and administering Codeine Sulfate Oral Solution to avoid dosing errors due to confusion between mg and mL which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

Always use the enclosed calibrated oral syringe or measuring cup when administering Codeine Sulfate Oral Solution to ensure the dose is measured and administered accurately. Do not use household teaspoons or tablespoons to measure Codeine Sulfate Oral Solution, as using a tablespoon instead of a teaspoon could lead to overdosage.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.2)]*.
- Monitor patients closely for respiratory depression, especially within the first 24 - 72 hours of initiating therapy and following dosage increases with Codeine Sulfate Oral Solution and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

2.2 Initial Dosage

Initiating Treatment with Codeine Sulfate Oral Solution

Initiate treatment with Codeine Sulfate Oral Solution in a dosing range of 15 to 60 mg (2.5 mL to 10 mL) every 4 hours as needed for pain.

Adult doses of Codeine Sulfate Oral Solution higher than 60 mg provide no further efficacy but are associated with greater adverse reactions. The maximum 24 hour dose is 360 mg.

Conversion from Other Opioids to Codeine Sulfate Oral Solution

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of Codeine Sulfate Oral Solution. It is safer to underestimate a patient's 24-hour Codeine Sulfate Oral Solution dosage than to overestimate the 24-hour Codeine Sulfate Oral Solution dosage and manage an adverse reaction due to overdose.

2.3 Titration and Maintenance of Therapy

Individually titrate Codeine Sulfate Oral Solution to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Codeine Sulfate Oral Solution to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.2)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Codeine Sulfate Oral Solution dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of Codeine Sulfate Oral Solution

When a patient who has been taking Codeine Sulfate Oral Solution regularly and may be physically dependent no longer requires therapy with Codeine Sulfate Oral Solution, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Codeine Sulfate Oral Solution in a physically-dependent patient *[see Warnings and Precautions (5.15), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral solution: each 5 mL of clear, reddish-orange to orange Codeine Sulfate Oral Solution USP contains codeine sulfate, 30 mg. The concentration of the 30 mg per 5 mL solution is 6 mg/mL.

4 CONTRAINDICATIONS

Codeine Sulfate Oral Solution is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.5)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.9)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*
- Hypersensitivity to codeine (e.g., anaphylaxis) *[see Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. Avoid dosing errors that may result from confusion between mg and mL when prescribing, dispensing, and administering Codeine Sulfate Oral Solution. Ensure that the dose is communicated clearly and dispensed accurately. Always use the enclosed calibrated oral syringe or measuring cup when administering Codeine Sulfate Oral Solution to ensure the dose is measured and administered accurately.

Do not use a teaspoon or a tablespoon to measure a dose. A household teaspoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the risk of mistakenly using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device. Health care providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage**.**

5.2 Addiction, Abuse, and Misuse

Codeine Sulfate Oral Solution contains codeine, a Schedule II controlled substance. As an opioid, Codeine Sulfate Oral Solution exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Codeine Sulfate Oral Solution. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Codeine Sulfate Oral Solution, and monitor all patients receiving Codeine Sulfate Oral Solution for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Codeine Sulfate Oral Solution, but use in such patients necessitates intensive counseling about the risks and proper use of Codeine Sulfate Oral Solution along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Codeine Sulfate Oral Solution. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.3 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, 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 *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Codeine Sulfate Oral Solution, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of Codeine Sulfate Oral Solution.

To reduce the risk of respiratory depression, proper dosing and titration of Codeine Sulfate Oral Solution are essential *[see Dosage and Administration (2.2, 2.3)]*. Overestimating the Codeine Sulfate Oral Solution dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of Codeine Sulfate Oral Solution, especially by children, can result in respiratory depression and death due to an overdose of codeine.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of Codeine Sulfate Oral Solution during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

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

Codeine Sulfate Oral Solution is contraindicated for post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

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 (8.4)]*.

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)]*.

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.

5.6 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Codeine Sulfate Oral Solution requires careful consideration of the effects on the parent drug, codeine, and the active metabolite, morphine.

- Cytochrome P450 3A4 Interaction

  The concomitant use of Codeine Sulfate Oral Solution with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of Codeine Sulfate Oral Solution with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal. Follow patients receiving Codeine Sulfate Oral Solution and any CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when Codeine Sulfate Oral Solution is used in conjunction with inhibitors and inducers of CYP3A4.

If concomitant use of a CYP3A4 inhibitor is necessary or if a CYP3A4 inducer is discontinued, consider dosage reduction of Codeine Sulfate Oral Solution until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

If concomitant use of a CYP3A4 inducer is necessary or if a CYP3A4 inhibitor is discontinued, consider increasing the Codeine Sulfate Oral Solution dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal [*see Drug Interactions (7)*].

- Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

  The concomitant use of Codeine Sulfate Oral Solution with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

  Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

  Follow patients receiving Codeine Sulfate Oral Solution and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when Codeine Sulfate Tablets are used in conjunction with inhibitors of CYP2D6.

  If concomitant use with a CYP2D6 inhibitor is necessary, follow the patient for signs of reduced efficacy or opioid withdrawal and consider increasing the Codeine Sulfate Oral Solution dosage. After stopping use of a CYP2D6 inhibitor, consider reducing the Codeine Sulfate Oral Solution dosage and follow the patient for signs and symptoms of respiratory depression or sedation [*see Drug Interactions (7)*].

5.7 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Codeine Sulfate Oral Solution with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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 (7)]*.

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 Codeine Sulfate Oral Solution are 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 (7), Patient Counseling Information (17)]*.

5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Codeine Sulfate Oral Solution in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease

Codeine Sulfate Oral Solution-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Codeine Sulfate Oral Solution *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating Codeine Sulfate Oral Solution and when Codeine Sulfate Oral Solution is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, codeine's active metabolite, including respiratory depression, coma, and confusion. Codeine Sulfate Oral Solution should not be used in patients taking MAOIs or within 14 days of stopping such treatment *[see Drug Interactions (7)]*.

5.10 Adrenal Insufficiency

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

5.11 Severe Hypotension

Codeine Sulfate Oral Solution may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been

compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Codeine Sulfate Oral Solution. In patients with circulatory shock, Codeine Sulfate Oral Solution may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Codeine Sulfate Oral Solution in patients with circulatory shock.

5.12 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Codeine Sulfate Oral Solution may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Codeine Sulfate Oral Solution.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Codeine Sulfate Oral Solution in patients with impaired consciousness or coma.

5.13 Risks of Use in Patients with Gastrointestinal Conditions

Codeine Sulfate Oral Solution is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The codeine in Codeine Sulfate Oral Solution may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.14 Increased Risk of Seizures in Patients with Seizure Disorders

The codeine in Codeine Sulfate Oral Solution may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Codeine Sulfate Oral Solution therapy.

5.15 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Codeine Sulfate Oral Solution. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

When discontinuing Codeine Sulfate Oral Solution, in a physically-dependent patient, gradually taper the dosage *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue Codeine Sulfate Oral Solution in these patients *[see Drug Abuse and Dependence (9.3)]*.

5.16 Risks of Driving and Operating Machinery

Codeine Sulfate Oral Solution may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Codeine Sulfate Oral Solution and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.2)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*

- Death Related to Ultra-rapid Metabolizers of Codeine *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*

The following adverse reactions associated with the use of codeine were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

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

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

Other less frequently observed adverse reactions expected from opioid analgesics, including Codeine Sulfate Oral Solution, 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

Serotonin Syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Codeine Sulfate Oral Solution.

Androgen Deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with Codeine Sulfate Oral Solution.

Table 1: Clinically Significant Drug Interactions with Codeine Sulfate Oral Solution

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of Codeine Sulfate Oral Solution and CYP3A4 inhibitors, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory

	depression, particularly when an inhibitor is added after a stable dose of Codeine Sulfate Oral Solution is achieved *[see Warnings and Precautions (5.6)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.
Intervention:	If concomitant use of CYP3A4 inhibitor is necessary, consider dosage reduction of Codeine Sulfate Oral Solution until stable drug effects are achieved. Monitor patients at for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the Codeine Sulfate Oral Solution dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of Codeine Sulfate Oral Solution and CYP3A4 inducers can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence *[see Warnings and Precautions (5.6)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, codeine plasma concentration may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use of a CYP3A4 inducer is necessary, follow the patient for reduced efficacy and signs of opioid withdrawal and consider increasing the Codeine Sulfate solution dosage as needed. If a CYP3A4 inducer is discontinued, consider Codeine Sulfate Oral Solution dosage reduction and monitor for signs of respiratory depression and sedation at frequent intervals.
Examples:	Rifampin, carbamazepine, phenytoin
Inhibitors of CYP2D6	
Clinical Impact:	Codeine is metabolized by CYP2D6 to form more potent morphine. The concomitant use of Codeine Sulfate Oral Solution and CYP2D6 inhibitors can increase the plasma concentration of codeine, but can decrease the plasma concentration of active metabolite morphine, particularly when an inhibitor is added after a stable dose of Codeine Sulfate Oral Solution is achieved *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.

	After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.
Intervention:	If concomitant use with a CYP2D6 inhibitor is necessary, or if a CYP2D6 inhibitor is discontinued after concomitant use, consider dosage adjustment of Codeine Sulfate Oral Solution and monitor patients closely at frequent intervals. If concomitant use with CYP2D6 inhibitors is necessary, follow the patient for reduced efficacy or signs and symptoms of opioid withdrawal and consider increasing the Codeine Sulfate Oral Solution as needed. After stopping use of a CYP2D6 inhibitor, consider reducing the Codeine Sulfate Oral Solution and monitor the patient for signs and symptoms of respiratory depression or sedation.
Examples	paroxetine, fluoxetine, bupropion, quinidine
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	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 (5.7)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Codeine Sulfate Oral Solution if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity

	(e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	Do not use Codeine Sulfate Oral Solution in patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of other opioids (such as oxycodone, hydrocodone, oxymorphone, hydrocodone, or buprenorphine) to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Codeine Sulfate Oral Solution and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Codeine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Codeine Sulfate Oral Solution and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Codeine Sulfate Oral Solution is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

Pregnancy Category C

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Codeine Sulfate Oral Solution are insufficient to inform a drug-associated risk for major birth defects and

miscarriage. In animal reproduction studies, codeine administration during organogenesis has been shown to produce delayed ossification in the offspring of mice at 1.4 times the maximum recommended human dose (MRHD) of 360 mg/day, embryolethal and fetotoxic effects in the offspring of rats and hamsters, at approximately 2 to 3 times the MRHD, and cranial malformations/cranioschisis in the offspring of hamsters between 2 and 8 times the MRHD [*see Data*].

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions: Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Codeine Sulfate Oral Solution is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Codeine Sulfate Oral Solution, can 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 dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

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

In a study in which pregnant hamsters were 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) during organogenesis cranial malformations (i.e., meningoencephalocele) in several fetuses were reported; as well as the observation of increases in the percentage of resorptions per litter. Doses of 50 and 150 mg/kg, bid resulted in fetotoxicity as demonstrated by decreased fetal body weight. In an earlier study in hamsters, single oral doses of 73 to 360 mg/kg level on Gestation Day 8 (oral; approximately 2 to 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) during organogensis, 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) administered between Gestation Day 7 and 12 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.

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 Lactation

Risk Summary

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 developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Codeine Sulfate Oral Solution and any potential adverse effects on the breastfed infant from Codeine Sulfate Oral Solution or from the underlying maternal condition.

Clinical Considerations

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. Infants exposed to codeine sulfate through breast milk should be monitored for excess sedation and respiratory depression. 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.

Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

8.4 Pediatric Use

The safety, effectiveness and the pharmacokinetics of Codeine Sulfate Oral Solution 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 Sulfate Oral Solution 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 Sulfate Oral Solution is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to codeine. In general, use caution when selecting a dosage 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.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Codeine Sulfate Oral Solution slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)]*.

Codeine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 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 with a lower than normal dosage of Codeine Sulfate Oral Solution or with longer dosing intervals and titrate slowly while monitoring signs of respiratory depression, sedation, and hypotension.

8.7 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 with a lower than normal dosage of Codeine Sulfate Oral Solution or with longer dosing intervals and titrate slowly while monitoring for signs of respiratory, sedation, and hypotension.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Codeine Sulfate Oral Solution contains codeine, a Schedule II controlled substance.

9.2 Abuse

Codeine Sulfate Oral Solution contains codeine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Codeine Sulfate Oral Solution can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.2)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. 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 healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Codeine Sulfate Oral Solution, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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.

Risks Specific to Abuse of Codeine Sulfate Oral Solution

Codeine Sulfate Oral Solution is intended for oral use only. Abuse of Codeine Sulfate Oral Solution poses a risk of overdose and death. The risk is increased with concurrent abuse of Codeine Sulfate Oral Solution with alcohol and other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infection diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance 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). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Codeine Sulfate Oral Solution should not be abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2.4)]*. If Codeine Sulfate Oral Solution is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and 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.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with Codeine Sulfate Oral Solution can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary

edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

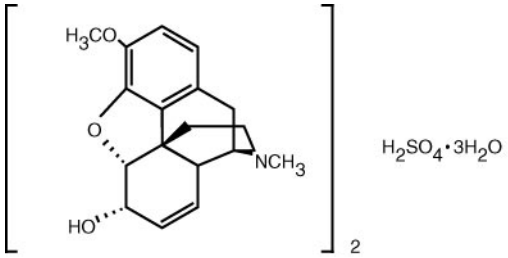
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to codeine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to codeine overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of codeine in Codeine Sulfate Oral Solution, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage 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. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Codeine Sulfate Oral Solution contains codeine, an opioid agonist, available for oral administration containing 30 mg per 5 mL (6 mg per mL) of codeine sulfate. The chemical name is Morphinan-6-ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-(5α,6α)-, sulfate (2:1) (salt), trihydrate. The molecular weight is 750.85 g/mol. Its molecular formula is $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$, and it has the following chemical structure.



Codeine sulfate trihydrate is a fine, white, crystalline powder which is soluble in water and insoluble in chloroform and ether.

Each 5 mL of oral solution contains 30 mg of codeine sulfate 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 relatively selective for the mu-opioid 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.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Codeine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Codeine 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Codeine 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Codeine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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 *[see Adverse Reactions (6)]*.

Effects on the 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. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of codeine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.2)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing codeine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

12.3 Pharmacokinetics

Absorption

Codeine is absorbed from the gastrointestinal tract with maximum plasma concentration occurring 60 minutes post administration. Administration of 15 mg of 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.

Food Effect: 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.

Distribution

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

Elimination

Codeine is metabolized by conjugation to codeine-6-glucuronide (70 to 80%), by *O*-demethylation to morphine (5 to 10%), and by *N*-demethylation to norcodeine (~10%). Approximately 90% of the total dose of codeine is excreted through the kidneys. The plasma half-lives of codeine and its metabolites have been reported to be approximately 3 hours.

Metabolism: About 70 to 80% of the administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (C6G) and via O-demethylation to morphine (about 5 to 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 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.

Excretion: 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Codeine Sulfate Oral Solution USP

Codeine Sulfate Oral Solution USP, 30 mg per 5 mL (6 mg/mL) is a clear, reddish-orange to orange solution available in one strength as follows:

30 mg per 5 mL Oral Solution

NDC 51224-300-10: 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Medication Errors

Instruct patients how to measure and take the correct dose of Codeine Sulfate Oral Solution, and to always use the enclosed oral syringe or measuring cup when administering Codeine Sulfate Oral Solution to ensure the dose is measured and administered accurately *[see Warnings and Precautions (5.1)]*.

If the prescribed concentration is changed, instruct patients on how to correctly measure the new dose to avoid errors which could result in accidental overdose and death.

Addiction, Abuse, and Misuse

Inform patients that the use of Codeine Sulfate Oral Solution, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.2)]*. Instruct patients not to share Codeine Sulfate Oral Solution with others and to take steps to protect Codeine Sulfate Oral Solution from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting Codeine Sulfate Oral Solution or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*. Instruct patients to take steps to store Codeine Sulfate Oral Solution securely and to properly dispose of unused Codeine Sulfate Oral Solution in accordance with the local state guidelines and/or regulations.

Ultra-Rapid Codeine Metabolizers

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 ultra-rapid codeine metabolizers 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 [*see Warnings and Precautions (5.5)]*.

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.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if Codeine Sulfate Oral Solution is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications *[see Drug Interactions 7)]*.

MAOI Interaction

Inform patients not to take Codeine Sulfate Oral Solution while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking Codeine Sulfate Oral Solution *[see Warnings and Precautions (5.9), Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.10)]*.

Important Administration Instructions

Instruct patients how to properly take Codeine Sulfate Oral Solution.

- Advise patients to always use the enclosed calibrated oral syringe/dosing cup when administering Codeine Sulfate Oral Solution to ensure the dose is measured and administered accurately *[see Warnings and Precautions (5.1)]*.
- Advise patients never to use household teaspoons or tablespoons to measure Codeine Sulfate Oral Solution.
- Advise patients not to adjust the dose of Codeine Sulfate Oral Solution without consulting a physician or other healthcare professional.
- If patients have been receiving treatment with Codeine Sulfate Oral Solution 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 [*see Dosage and Administration (2.4)*, *Warnings and Precautions (5.15)*].

Hypotension

Inform patients that Codeine Sulfate Oral Solution may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.11)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in Codeine Sulfate Oral Solution. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4)*, *Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome: Inform female patients of reproductive potential that prolonged use of Codeine Sulfate Oral Solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity: Inform female patients of reproductive potential that Codeine Sulfate Oral Solution can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

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) [*see Use in Specific Populations (8.2)*].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)].*

Driving or Operating Heavy Machinery

Inform patients that Codeine Sulfate Oral Solution may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.16)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Disposal of Unused Codeine Sulfate Oral Solution

Advise patients to properly dispose of unused Codeine Sulfate Oral Solution. Advise patients to throw the drug in the household trash following these steps. 1) Remove them from their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter (this makes the drug less appealing to children and pets, and unrecognizable to people who may intentionally go through the trash seeking drugs). 2) Place the mixture in a sealable bag, empty can, or other container to prevent the drug from leaking or breaking out of a garbage bag, or to dispose of in accordance with local state guidelines and/or regulations.

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Medication Guide

Codeine Sulfate (KOE-deen SUL-fate) Oral Solution USP, CII

Codeine Sulfate Oral Solution is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage mild to moderate pain, where treatment with an opioid is appropriate, and when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death

Important information about Codeine Sulfate Oral Solution:

- **Get emergency help right away if you take too much Codeine Sulfate Oral Solution (overdose).** When you first start taking Codeine Sulfate Oral Solution, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking Codeine Sulfate Oral Solution 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.
- Never give anyone else your Codeine Sulfate Oral Solution. They could die from taking it. Store Codeine Sulfate Oral Solution away from children and in a safe place to prevent stealing or abuse. Selling or giving away Codeine Sulfate Oral Solution is against the law.

Do not take Codeine Sulfate Oral Solution if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- an allergy to Codeine Sulfate Oral Solution or any of the ingredients
- Do not give Codeine Sulfate Oral Solution to a child to treat pain after tonsillectomy and/or adenoidectomy surgery.

Before taking Codeine Sulfate Oral Solution, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- have been told by your healthcare provider that you are a “rapid metabolizer” of certain medicines

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of codeine sulfate during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.

- **breastfeeding.** When taking Codeine Sulfate Oral Solution, some or all of it changes into morphine in your body. In some women, this may happen very quickly. Codeine and morphine pass into your breast milk. A large amount of morphine can cause your baby to die.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking codeine sulfate with certain other medicines can cause serious side effects that could lead to death.

When taking Codeine Sulfate Oral Solution:

- Do not change your dose. Take Codeine Sulfate Oral Solution exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- See the detailed Instructions for Use for information about how to take Codeine Sulfate Oral Solution.
- Always use the calibrated oral syringe or measuring cup that comes with Codeine Sulfate Oral Solution to correctly measure your dose. Never use a household teaspoon or tablespoon to measure Codeine Sulfate Oral Solution.
- Take your prescribed dose every 4 hours as needed. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking Codeine Sulfate Oral Solution regularly, do not stop taking Codeine Sulfate Oral Solution without talking to your healthcare provider.
- After you stop taking Codeine Sulfate Oral Solution, dispose the unused Codeine Sulfate Oral Solution in accordance with the local state guidelines and/or regulations.

While taking Codeine Sulfate Oral Solution DO NOT:

- Drive or operate heavy machinery, until you know how codeine sulfate affects you. Codeine sulfate can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with codeine sulfate may cause you to overdose and die.

The possible side effects of Codeine Sulfate Oral Solution:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- If you are a nursing mother taking Codeine Sulfate Oral Solution and your breastfeeding baby has: increased sleepiness, confusion, difficulty breathing, shallow breathing, limpness, or difficulty breastfeeding.

These are not all the possible side effects of codeine sulfate. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Instructions for Use

Codeine Sulfate Oral Solution USP (CII)
(koh-deen)

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.

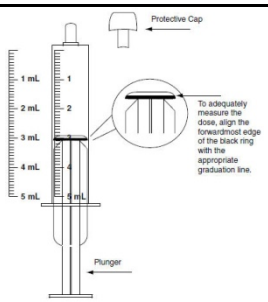

Figure 1

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

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