CODEINE SULFATE- codeine sulfate tablet
Roxane Laboratories, Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Codeine sulfate tablets safely and effectively. See full prescribing information for Codeine sulfate tablets.
Initial U.S. Approval: 1950

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE
See full prescribing information for complete boxed warning.

INDICATIONS AND USAGE

Codeine sulfate is an opioid analgesic indicated for the relief 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 up to every 4 hours as needed. (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)

DOSAGE FORMS AND STRENGTHS

Codeine sulfate tablets: 15 mg, 30 mg, and 60 mg. (3)

CONTRAINDICATIONS

- Postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy (4)
- Hypersensitivity to codeine sulfate 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, including respiratory depression, hypotension, profound sedation, coma, or death 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: In 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, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Roxane Laboratories, Inc. at 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. Use with

caution in reduced dosages to persons receiving MAO inhibitors or tricyclic antidepressants. (7.4)

- Metabolic enzymes: Concomitant use of cytochrome P-450 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: 9/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 relief 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. Physicians should 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.

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, addiction or diversion, including a prior history of abuse, addiction or diversion.

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 control 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 physician, other members of the healthcare team, the patient, and the caregiver/family.

2.2 Initiation of Therapy

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

The initial dose should be titrated based upon the individual patient's response to their initial dose of codeine. This dose can then be adjusted 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, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

3 DOSAGE FORMS AND STRENGTHS

Each 15 mg tablet for oral administration contains 15 mg of codeine sulfate, USP. It is a white, biconvex tablet scored on one side, with strength-indicating number "15" debossed on the scored side and product identification number "54 613" debossed on the other side.

Each 30 mg tablet for oral administration contains 30 mg of codeine sulfate, USP. It is a white, biconvex tablet scored on one side, with strength-indicating number "30" debossed on the scored side and product identification number "54 783" debossed on the other side.

Each 60 mg tablet for oral administration contains 60 mg of codeine sulfate, USP. It is a white, biconvex tablet scored on one side, with strength-indicating number "60" debossed on the scored side and product identification number "54 412" debossed on the other side.

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 [CYP2D6] 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 (10.1)]*.

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. Opioid related 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. Opioids, including codeine sulfate, should be used 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. Alternative non-opioid analgesics should be considered, and codeine sulfate should be employed only under careful medical supervision at the lowest effective dose in such patients *[see Overdosage (10.1)]*.

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.

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.

Misuse and abuse of codeine sulfate poses a significant risk to the abuser that could result in overdose and death. Codeine may be abused by crushing, chewing, snorting or injecting the product *[see Drug Abuse and Dependence (9)]*.

Concerns about abuse and addiction 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, produce adverse reactions which may obscure the clinical course of 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.

Codeine sulfate should be administered 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

Codeine sulfate should not be administered 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.

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

Codeine sulfate should be used in 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

As with other opioids, codeine sulfate should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyrodism, Addison's disease, prostatic hypertrophy or urethral stricture *[see Use in Specific Populations (8)]*. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

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.

5.10 Driving and Operating Machinery

Patients should be cautioned 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.

Patients should also be cautioned about the potential combined effects of codeine sulfate with other CNS depressants, including 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 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 tablets 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

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should NOT be administered 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 including codeine sulfate, may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

7.4 Antidepressants

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

7.5 Metabolic Enzymes

Patients taking cytochrome P-450 enzyme inducers or inhibitors may demonstrate an altered response to codeine, therefore analgesic activity should be monitored. Codeine sulfate is metabolized by the cytochrome P-450 3A4 and 2D6 isoenzymes *[see Clinical Pharmacology (12.3)]*. The concurrent use of drugs that preferentially induce codeine *N*-demethylation (cytochrome P-450 3A4) may increase the plasma concentrations of codeine's inactive metabolite norcodeine. Drugs that are strong inhibitors of codeine *O*-demethylation (cytochrome P-450 2D6) may decrease the plasma concentrations of codeine's active metabolites, morphine and morphine-6-glucuronide. The contribution of these active metabolites to the overall analgesic effect of codeine is not fully understood, but should be considered.

7.6 Drug-Laboratory Test Interaction

Codeine sulfate tablets 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 2-4 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 embrytoxicity 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 Nonclinical Toxicology (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 placental barrier and may produce respiratory depression and psycho-physiologic effects in neonates. 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. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Opioid analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required *[see Overdosage (10.2)]*. A specific opioid antagonist, such as naloxone or nalmefene, should be 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 breastfeeding *[see Warnings and Precautions (5.1)]*.

8.4 Pediatric Use

The safety and effectiveness and the pharmacokinetics of codeine sulfate in pediatric patients below the age of 18 have not been established. FDA has not required pediatric studies in ages birth to one month because there is evidence strongly suggesting that codeine would be ineffective in this pediatric group since the metabolic pathways to metabolize codeine are not mature.

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. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, 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). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

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 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). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

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 of 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, miosis (mydriasis may occur in terminal narcosis or severe hypoxia), skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

Codeine sulfate 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

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation as necessary. Supportive measures (including oxygen and vasopressors) should be employed 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 opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression resulting from overdosage or unusual sensitivity to opiate agonists, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see prescribing information for naloxone hydrochloride) should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression secondary to codeine sulfate

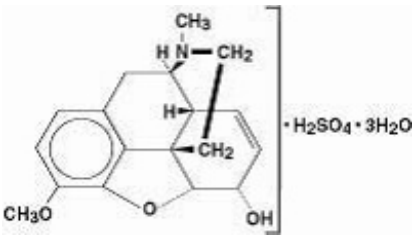
overdose.

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. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and titrated with smaller than usual doses.

11 DESCRIPTION

Chemically, codeine is Morphinan-6-ol,7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-(5α,6α)-, sulfate (2:1) (salt), trihydrate. Its empirical formula is $C_{18}H_{21}NO_3$ and its molecular weight is 299.36.

Its structure is as follows:



Each tablet contains 15, 30, or 60 mg of codeine sulfate and the following inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, pregelatinized starch, and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Codeine sulfate is an opioid analgesic, 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 sulfate 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. Some other CNS effects of codeine include anxiolysis, euphoria, and feelings of relaxation. Codeine sulfate causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Codeine sulfate and other related opioids depress the cough reflex by direct effect on the cough center in the medulla. Codeine sulfate 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

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 such as codeine sulfate 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

Codeine has 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 concentrations do not correlate with brain concentration 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 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) 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 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. Similiarly 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 mutatgenic 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 bid of codeine (PO; 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 (PO; 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 (PO; 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 (SC; 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

15 mg Tablet: white, biconvex tablets scored on one side, with strength-indicating number “15” debossed on the scored side and product identification number “54 613” debossed on the other side.

Unit dose, 25 tablets per blister card

NDC 0054-8155-24: 4 Cards per Carton

30 mg Tablet: white, biconvex tablets scored on one side, with strength-indicating number “30” debossed on the scored side and product identification number “54 783” debossed on the other side.

Unit dose, 25 tablets per blister card

NDC 0054-4156-24: 4 Cards per Carton

NDC 0054-0244-25: Bottles of 100 Tablets

60 mg Tablet: white, biconvex tablets scored on one side, with strength-indicating number “60” debossed on the scored side and product identification number “54 412” debossed on the other side.

NDC 0054-4157-25: Bottles of 100 Tablets

Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture and light.

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

Blisters are not child-resistant. Use child-resistant closure if dispensing to outpatient.

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

17 PATIENT COUNSELING INFORMATION

- Advise patients that codeine sulfate is a narcotic pain reliever and may be habit forming. It 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 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 that the dose of codeine sulfate should not be adjusted without consulting with your physician.
- 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 such as driving a car or operating machinery.

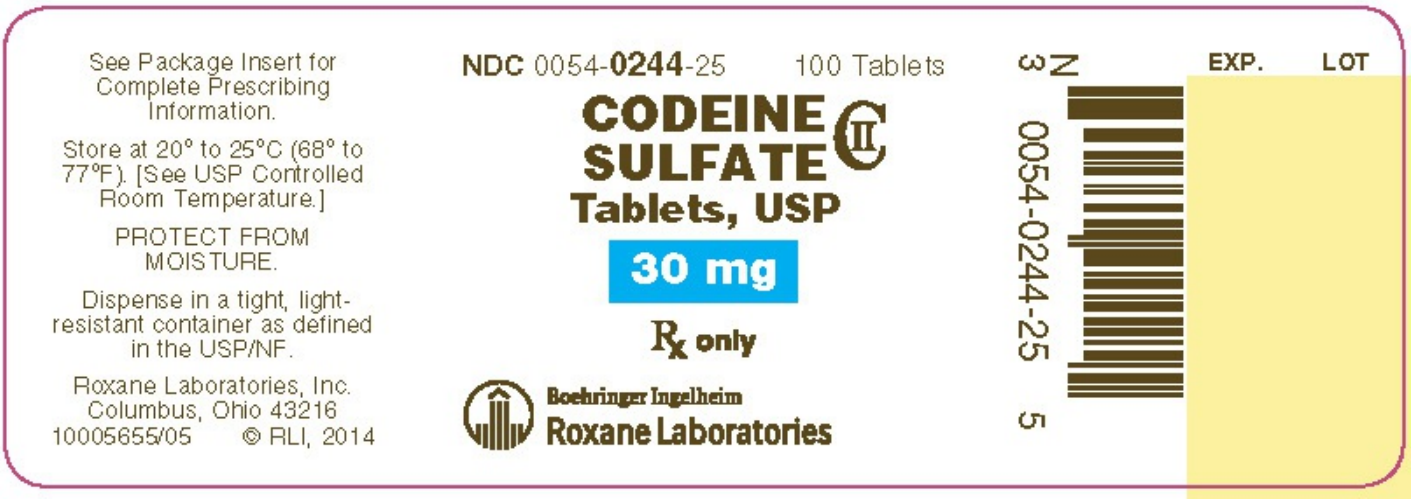
- Advise patients started on codeine sulfate or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected. Advise patients not to combine codeine sulfate with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
- Advise patients that codeine sulfate is a potential drug of abuse, and should be protected 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.
- If patients have been receiving treatment with codeine sulfate for more than a few weeks and cessation of therapy is indicated, they should be counseled on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. The physician should provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Women of childbearing potential who become or are planning to become pregnant should consult a physician prior to initiating or continuing therapy with codeine sulfate.
- Safe use in pregnancy has not been established. Prolonged use of opioid analgesics during pregnancy may cause fetal/neonatal physical dependence, and neonatal withdrawal may occur.

10005657/06

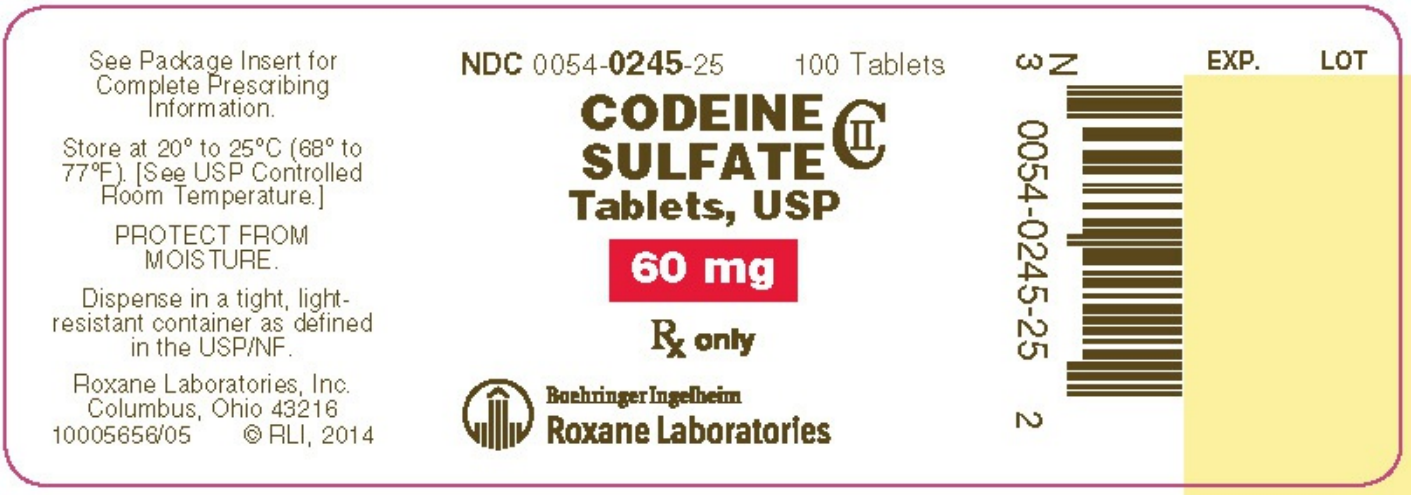
Revised September 2014

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL



CODEINE SULFATE

codeine sulfate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0054-0243
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CODEINE SULFATE (CODEINE ANHYDROUS)	CODEINE SULFATE	15 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE	

CELLULOSE, MICROCRYSTALLINE	
STARCH, CORN	
STEARIC ACID	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	15;54;613
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-0243-24	4 in 1 BOX, UNIT-DOSE		
1		25 in 1 BLISTER PACK; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022402	10/01/2009	

CODEINE SULFATE

codeine sulfate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0054-0245
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CODEINE SULFATE (CODEINE ANHYDROUS)	CODEINE SULFATE	60 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
STARCH, CORN	
STEARIC ACID	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	60;54;412
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0054-0245-25	100 in 1 BOTTLE; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022402	10/01/2009	

CODEINE SULFATE

codeine sulfate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0054-0244
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CODEINE SULFATE (CODEINE ANHYDROUS)	CODEINE SULFATE	30 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
STARCH, CORN	
STEARIC ACID	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	30;54;783
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-0244-24	4 in 1 BOX, UNIT-DOSE		
1		25 in 1 BLISTER PACK; Combination Product Type = C112160		
2	NDC:0054-0244-25	100 in 1 BOTTLE; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022402	10/01/2009	

Labeler - Roxane Laboratories, Inc (833490464)

Registrant - Roxane Laboratories, Inc (833490464)

Establishment

Name	Address	ID/FEI	Business Operations
Boehringer Ingelheim Roxane Inc		058839929	MANUFACTURE(0054-0243, 0054-0245, 0054-0244)

Revised: 9/2014 Roxane Laboratories, Inc