HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS safely and effectively. See full prescribing information for CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS.

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, CIII

Initial U.S. Approval: 1985

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

See full prescribing information for complete boxed warning.
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 (5.1)*].

INDICATIONS AND USAGE

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is a combination of codeine phosphate, an opiate agonist antitussive, and chlorpheniramine maleate, a histamine-1 (H_1) receptor antagonist indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold. (1)

Important Limitations of Use

Not indicated for pediatric patients under 18 years of age *[see Use in Special Population (8.4)*

DOSAGE AND ADMINISTRATION

- Adults and children 18 years of age and older: 1 tablet every 12 hours, not to exceed 2 doses in 24 hours. (2.1)

DOSAGE FORMS AND STRENGTHS

Extended release (ER) tablet: contains 54.3 mg of codeine phosphate (equivalent to 40 mg of codeine) and 8 mg of chlorpheniramine maleate (equivalent to 5.6 mg of chlorpheniramine). (3)

CONTRAINDICATIONS

Post-operative pain management in children undergoing tonsillectomy and/or adenoidectomy. (4)

- Patients with known hypersensitivity to codeine, chlorpheniramine, or any of the product components of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. (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)
- Dose-related respiratory depression: Use with caution. (5.2)
- Drug dependence: Prescribe with caution that is appropriate to the use of other opioids. (5.3)
- Head injury, intra-cranial lesions, or increased intracranial pressure: Avoid in patients with head injury, intra-cranial lesions, or increased intracranial pressure. (5.4)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating heavy machinery. Avoid concurrent use of alcohol or other central nervous system depressants. (5.5)
- Acute abdominal conditions: Use with caution in patients with acute abdominal conditions. (5.7)
- Special risk patients: Caution in elderly patients and those with asthma, persistent or chronic cough, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. (5.8)

ADVERSE REACTIONS

Common adverse reactions of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS include: Nausea and vomiting, constipation, abdominal distension, abdominal pain, blurred vision, diplopia, visual disturbances, confusion, dizziness, depression, drowsiness, sedation, headache, euphoria, facial dyskinesia, feeling faint, light-headedness, general feeling of discomfort or illness, excitability, nervousness, agitation, restlessness, somnolence, insomnia, dyskinesia, irritability, tremor. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Nexgen Pharma, Inc. at 888-710-0006 or go to www.nexgenpharma.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants: may cause additive CNS depression. (7.1)
- MAOIs or tricyclic antidepressants: may increase the effect of either the antidepressant or codeine. (7.2)
- Anticholinergic drugs: Use with caution. Additive adverse effects resulting from cholinergic blockage (e.g., xerostomia, blurred vision, or constipation) may occur. (7.3)
- Inhibitors or inducers of metabolic enzymes: Concomitant use of cytochrome P450 2D6 and 3A4 enzyme inhibitors or inducers may result in an altered response to codeine, monitor antitussive activity. Chlorpheniramine may inhibit the hepatic metabolism of phenytoin, monitor phenytoin toxicity.(7.4)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

- Labor: Use of codeine during labor can produce respiratory depression in the neonate. (8.2)
- 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 patients: Safety and effectiveness of this drug product has not been established for patients under 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2015

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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 [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older.

Important Limitations of Use

Not indicated for pediatric patients under 18 years of age *[see Use in Special Population (8.4)]*

2 DOSAGE AND ADMINISTRATION

2.1 Adults 18 Years of Age and Older

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be administered orally at a dosage of one tablet every 12 hours, not to exceed 2 tablets in 24 hours.

3 DOSAGE FORMS AND STRENGTHS

Extended release tablets: Each tablet contains 54.3 mg of codeine phosphate (equivalent to 40 mg of codeine) and 8 mg of chlorpheniramine maleate (equivalent to 5.6 mg of chlorpheniramine). Each tablet is white to off-white, uncoated, round, debossed with **NXG** on one side and **CC** on the other side.

4 CONTRAINDICATIONS

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is contraindicated in:

- Postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.1)]*.
- Patients with known hypersensitivity to codeine, chlorpheniramine or any of the inactive ingredients of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. Persons known to be hypersensitive to certain other opioids may exhibit cross-sensitivity to codeine.

5 WARNINGS AND PRECAUTIONS

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

Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine. *[see Use in Specific Populations (8.3)]*

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). *[see Overdosage (10)]*

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

When prescribing codeine-containing drugs, healthcare professionals 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)]*

5.2 Respiratory Depression

Codeine, one of the active ingredients in CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, produces dose-related respiratory depression by directly acting on brain stem respiratory centers.

Overdose of codeine in adults has been associated with fatal respiratory depression, and the use of codeine in children has been associated with fatal respiratory depression. Exercise caution when administering CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS because of the potential for respiratory depression. If respiratory depression occurs, discontinue CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS and use naloxone hydrochloride when indicated to antagonize the effect and other supportive measures as necessary. *[see Overdosage (10)]*

5.3 Drug Dependence

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. Prescribe and administer CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS with the same degree of caution appropriate to the use of other opioid drugs. *[see Drug Abuse and Dependence (9.2, 9.3)]*

5.4 Head Injury and Increased Intracranial Pressure

The respiratory depression effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions that may obscure the clinical course of patients with head injuries. The

use of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be avoided in these patients.

5.5 Activities Requiring Mental Alertness

Codeine and chlorpheniramine, the active ingredients in CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, may produce marked drowsiness and 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 to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. Concurrent use of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.6 Obstructive Bowel Disease

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

5.7 Acute Abdominal Conditions

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be used with caution in patients with acute abdominal conditions since the administration of codeine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. The concurrent use of other anticholinergics with codeine may produce paralytic ileus. *[see Drug Interactions (7.3)]*

5.8 Special Risk Patients

As with other opioids, CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be used with caution in elderly or debilitated patients and those with asthma, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

6 ADVERSE REACTIONS

Use of codeine, an opioid, may result in the following:

- Respiratory depression *[see Warnings and Precautions (5.2) and Overdosage (10)]*
- Drug dependence *[see Warnings and Precautions (5.3)]*
- Increased intracranial pressure *[see Warnings and Precautions (5.4)]*
- Decreased mental alertness with impaired mental and/or physical abilities *[see Warnings and Precautions (5.5)]*
- Paralytic ileus *[see Warnings and Precautions (5.7)]*

Use of chlorpheniramine, an antihistamine, may result in:

- Decreased mental alertness with impaired mental and/or physical abilities *[see Warnings and Precautions (5.5)]*

Adverse reactions listed below have been reported in the literature for codeine and chlorpheniramine and may be expected to occur with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. Also included are events that occurred during clinical pharmacokinetic studies (in a total of 66 healthy adult volunteers with either single or multiple dose exposure) with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS and judged by the investigator to be related to study treatment. Because these reactions may be 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.

Allergic: Allergic laryngospasm, nasal stuffiness, bronchospastic allergic reaction, hives, itching, swelling of face.

Body as a whole: Asthenia, feeling of relaxation, redness or flushing of the face, unusual tiredness, weakness.
Cardiovascular: Fast, or slow heartbeat, hypertension, hypotension, orthostatic hypotension, palpitations, shock-like state, syncope.

Dermatological System: Skin rash, pruritus, erythema, urticaria, excessive perspiration, dermatitis.

Endocrine System: Changes in glucose utilization, decreased lactation, early menses, glycosuria, gynecomastia, hypoglycemia, increased appetite, increased libido, pheochromocytoma stimulation.

Gastrointestinal System: Nausea and vomiting,, constipation, abdominal distension, abdominal pain, acute pancreatitis, dry mouth, dyspepsia, epigastric distress, loss of appetite, diarrhea, gastro-esophageal reflux, gastrointestinal hypomotility.

Genitourinary System: Ureteral spasm, urinary retention, dysuria, urinary frequency, urinary hesitancy, irritative bladder symptom.

Nervous System: Blurred vision, diplopia, visual disturbances, confusion, dizziness, depression, drowsiness, sedation, headache, euphoria, facial dyskinesia, false sense of well-being, feeling faint, lightheadedness, general feeling of discomfort or illness, excitability nervousness, agitation, restlessness, somnolence, insomnia, dyskinesia, irritability, tremor.

Respiratory: Dryness of the pharynx and respiratory passages, laryngismus, atelectasis, wheezing, troubled breathing, respiratory depression, hiccups.

Special Senses: labyrinthitis, tinnitus, vertigo, hypermetropia, lacrimation increased, mydriasis, photophobia.

7 DRUG INTERACTIONS

7.1 Opioids, Antihistamines, Antipsychotics, Anti-anxiety Agents, or Other CNS Depressants (Including Alcohol)

The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS may cause an additive CNS depressant effect and should be avoided.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Do not prescribe CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS if the patient is taking a monoamine oxidase inhibitor (MAOI) (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping a MAOI drug. The use of MAOIs or tricyclic antidepressants with codeine preparations may increase the effect of either the antidepressant or codeine.

7.3 Anticholinergic Drugs

Codeine and chlorpheniramine should be administered cautiously to persons receiving other anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects.

Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, or constipation) may occur when anticholinergic drugs are administered with chlorpheniramine.

7.4 Inhibitors or Inducers of Metabolic Enzymes

Codeine is metabolized by the CYP2D6 and CYP3A4 isoenzymes *[see Pharmacokinetics (12.3)]*. The concurrent use of drugs that preferentially induce codeine N-demethylation (via CYP3A4) may increase the plasma concentrations of

codeine's inactive metabolite norcodeine. Drugs that inhibit codeine O-demethylation (via CYP2D6), may decrease the plasma concentration of codeine's active metabolites, morphine and morphine-6-glucuronide. The contribution of these active metabolites to the overall antitussive effect of codeine is not known, but should be considered.

Adverse event reports in the literature suggest a possible drug interaction involving increased serum phenytoin levels and phenytoin toxicity when chlorpheniramine and phenytoin are co-administered. The exact mechanism for this interaction is not known, however it is believed that chlorpheniramine may inhibit the hepatic metabolism of phenytoin. Patients should be monitored for evidence of phenytoin toxicity such as ataxia, hyperreflexia, nystagmus and tremor when these two drugs are co-administered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

There are no adequate and well-controlled studies of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER Tablets in pregnant women.

Reproductive toxicity studies have not been conducted with CODEINE AND CHLORPHENIRAMINE MALEATE ER TABLETS; however, studies are available with individual active ingredients or related active ingredients. Because animal reproduction studies are not always predictive of human response, CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Codeine:

Codeine has embryolethal and fetotoxic effects in rats. In a study in which pregnant rats were dosed throughout organogenesis, a dose approximately 15 times the maximum recommended human daily dose (MRHDD; on a mg/m^2 basis at an oral maternal dose of 120 mg/kg/day) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of maternal toxicity.

In studies in which rabbits and mice were dosed throughout organogenesis, codeine at doses approximately 7 and 35 times the MRHDD (on a mg/m^2 basis at 30 and 600 mg/kg/day, respectively) produced no adverse developmental effects.

Chlorpheniramine:

A retrospective study found a small, but statistically significant, association between maternal use of chlorpheniramine and inguinal hernia and eye or ear anomalies in children. Other retrospective studies have found that the frequency of congenital anomalies, in general, was not increased among offspring of women who took chlorpheniramine during pregnancy. The significance of these findings to the therapeutic use of chlorpheniramine in human pregnancy is not known.

In studies with chlorpheniramine in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 25 and 30 times the MRHDD on a mg/m^2 basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, a dose approximately 9 times the MRHDD (on a mg/m^2 basis at an oral maternal dose of 20 mg/kg/day) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed with approximately 9 times the MRHDD (on a mg/m^2 basis at an oral parental dose of 10 mg/kg/day) prior to mating.

Nonteratogenic Effects

Codeine:

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

8.2 Labor and Delivery

As with all opioids, administration of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

8.3 Nursing Mothers

Caution should be exercised when CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is administered to nursing mothers. Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breast-feeding *[see Warnings and Precautions (5.1)]*.

Chlorpheniramine is excreted in human milk. The clinical significance is unknown; however, the anticholinergic action of chlorpheniramine may suppress lactation if taken prior to nursing.

8.4 Pediatric Use

Safety and effectiveness of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS in patients under 18 years of age have not been established. The use of codeine in children has been associated with fatal respiratory depression. *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical efficacy and safety studies have not been conducted with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. Other reported clinical experience with the individual active ingredients of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be made with caution, 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

Pharmacokinetics of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS has not been characterized in renal impairment subjects.

Both codeine phosphate and chlorpheniramine maleate are cleared substantially by the kidney. As such, impaired renal function could potentially lead to the risk of decreased clearance and thereby increased retention or systemic levels of both these drugs. CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be used with caution in patients with severe renal impairment.

8.7 Hepatic Impairment

Pharmacokinetics of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS has not been characterized in hepatic impairment subjects. Both codeine and chlorpheniramine maleate are extensively metabolized by liver before elimination from the body. As such, impaired hepatic function could potentially lead to the risk of decreased metabolism and thereby increased systemic levels of both these drugs. CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be used with caution in patients with severe hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is a Schedule III controlled prescription product containing codeine and should be prescribed and administered with caution.

9.2 Abuse

Codeine can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, and it should be prescribed and administered with the same degree of caution appropriate to the use of other opioid drugs.

9.3 Dependence

Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS should be prescribed and administered with caution.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy.

10 OVERDOSAGE

No human overdosage data are available for CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS.

<u>Codeine</u>

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

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

Chlorpheniramine

Manifestations of chlorpheniramine overdosage may vary from central nervous system depression to stimulation. Central toxic effects are characterized by agitation, anxiety, delirium, disorientation, hallucinations, hyperactivity, sedation, and seizures. Severe overdosage may produce coma, medullary paralysis, and death. Peripheral toxicity includes hypertension, tachycardia, dysrhythmias, vasodilation, hyperpyrexia, mydriasis, urinary retention, and diminished gastrointestinal motility. Dry mouth, pharynx, bronchi, and nasal passages may be observed.

Impaired secretion from sweat glands following toxic doses of drugs with anticholinergic side effects may predispose to hyperthermia.

An adult ingested 400 mg chlorpheniramine with no reported serious adverse effects. Toxic psychosis, a possible class effect from overdose of sedating antihistamines, has been reported with accidental overdose of chlorpheniramine.

Treatment of overdosage consists of discontinuation of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS together with institution of appropriate therapy.

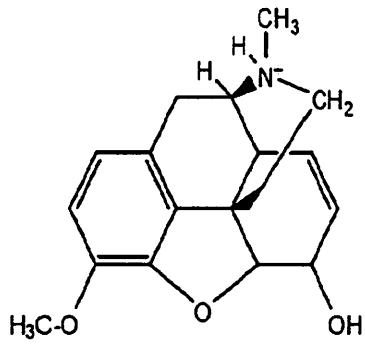
Give primary attention to re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression that may result from overdosage or unusual sensitivity to opioids including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory or circulatory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

Hemodialysis is not routinely used to enhance the elimination of codeine or chlorpheniramine from the body. Urinary excretion of chlorpheniramine is increased when the pH of the urine is acidic; however, acid diuresis is NOT recommended to enhance elimination in overdose, as the risks of acidemia and acute tubular necrosis in patients with rhabdomyolysis far outweigh any potential benefits.

11 DESCRIPTION

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS are extended release tablets that contain 54.3 mg of codeine phosphate (equivalent to 40 mg of codeine) and 8 mg of chlorpheniramine maleate (equivalent to 5.6 mg of chlorpheniramine)..

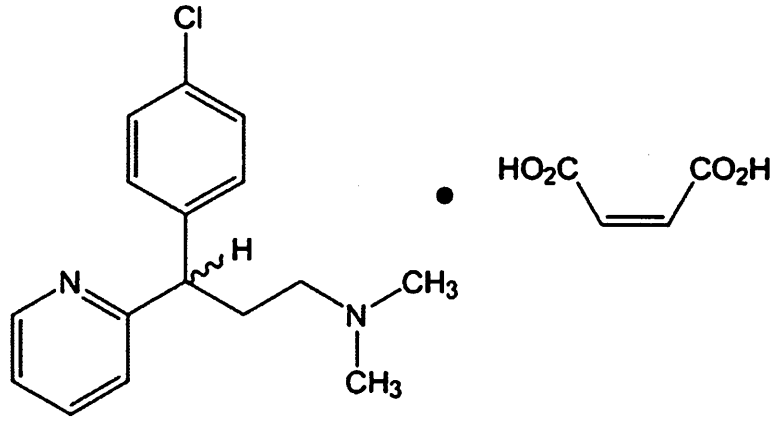
Codeine phosphate [morphine3methyl ether phosphate (1:1) (salt)] hemihydrate, is a narcotic analgesic and antitussive. It has the following structural formula:



$H_3PO_4 \cdot 1/2\ H_2O$

Codeine Phosphate Hemihydrate
$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$
MW 406.37

Chlorpheniramine maleate is 2-pyridinepropanamine, γ-(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1) and has the following chemical structure:



Chlorpheniramine Maleate
$C_{16}H_{19}ClN_2 \bullet C_4H_4O_4$
Molecular weight = 390.86

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS are white to off-white, uncoated, standard round extended release matrix tablets.

Other ingredients: hypromellose, lactose monohydrate, cellulose microcrystalline, polysorbate 80, magnesium stearate, and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Codeine: Codeine is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of morphine. The precise mechanism of action of codeine and other opiates is not known; however, codeine is believed to act centrally on the cough center. In excessive doses, codeine will depress respiration. Codeine can produce miosis, euphoria, and physical and physiological dependence.

Chlorpheniramine: Chlorpheniramine is a propylamine derivative antihistamine (H1-receptor antagonist) of the alkylamine class that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

12.3 Pharmacokinetics

Absorption

Pharmacokinetic (PK) parameters (Mean ± SD) for CODEINE AND CHLORPHENIRAMINE MALEATE EXTENDED RELEASE TABLETS in fasting, healthy volunteers are shown in the table below.

PK Parameter	Single-dose		Multiple-dose (BID for 6.5 days)	
	Codeine Mean (± SD)	Chlorpheniramine Maleate Mean (± SD)	Codeine Mean (± SD)	Chlorpheniramine Maleate Mean (± SD)
Tmax (h) (Range)	3 (2-12)	6 (4-12)	3 (2-5)	5 (3-7)
Cmax (ng/mL)	46 (11)	9 (3)	74 (19)	39 (13)
AUCinf (ng.h/mL) for single-dose OR AUC12 (ng.h/mL) for multiple-dose	383 (99)	312 (137)	505 (143)	405 (145)
Half life (h)	4 (1)	21 (7)	Not determined	Not determined

Food Effect

The presence of a high-fat, high-calorie meal did not significantly impact the PK parameters of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS.

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. About 7-25% of codeine, reportedly, is bound to plasma proteins. Codeine passes the blood brain barrier and the placental barrier. Small amounts of codeine and its metabolite, morphine, are transferred to human breast milk.

Chlorpheniramine is widely distributed throughout the tissues of the body, including the central nervous system. It reportedly has an apparent steady-state volume of distribution of approximately 3.2 L/kg in adults and children and is about 70% bound to plasma proteins. Chlorpheniramine and its metabolites likely cross the placental barrier and are excreted into human breast milk.

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 P-450 (CYP) 2D6 and CYP3A4 are the major enzymes mediating O-demethylation and N-demethylation of codeine respectively. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. Morphine and its M6 glucuronide conjugate are pharmacologically active. Whether C6G has pharmacological activity is unknown. Norcodeine and M3 glucuronide conjugate of morphine are generally not considered to be pharmacologically active.

Chlorpheniramine is rapidly and extensively metabolized via demethylation in the liver, forming mono- and didesmethyl derivatives. Oxidative metabolism of chlorpheniramine is catalyzed by cytochrome P-450 2D6.

Elimination

Approximately 90% of the total dose of codeine is excreted through the kidneys, of which approximately 10% is unchanged codeine. Plasma half-life of codeine was observed to be about 4 hours with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS.

Chlorpheniramine and its metabolites are primarily excreted through the kidneys, with large individual variation. Urinary excretion depends on urine pH and flow rate. Plasma half-life of chlorpheniramine was observed to be about 21 hours with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS; however, published information is available for the active ingredients

Codeine: In 2-year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 9 and 25 times, respectively, the MRHDD dose for adults and children on a mg/m2 basis).

Codeine was not mutagenic in the in vitro bacterial reverse mutation assay or clastogenic in the in vitro Chinese hamster ovary (CHO) cell chromosomal aberration assay.

Fertility studies with codeine have not been conducted.

Chlorpheniramine: In 2-year studies in F344/N rats and B6C3F1 mice, chlorpheniramine maleate showed no evidence of tumorigenicity when administered 5 days/week at oral doses up to 30 and 50 mg/kg/day, respectively (approximately 25 and 20 times, respectively, the MRHDD on a mg/m2 basis).

Chlorpheniramine maleate was not mutagenic in the in vitro bacterial reverse mutation assay or the in vitro mouse lymphoma forward mutation assay. Chlorpheniramine maleate was clastogenic in the in vitro CHO cell chromosomal aberration assay.

Chlorphenirimaleate had no effects on fertility in rats and rabbits at oral doses approximately 25 and 30 times, respectively, the MRHDD on a mg/m2 basis.

14 CLINICAL STUDIES

The efficacy of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is based on previously established findings of effectiveness of codeine and chlorpheniramine at the proposed doses.

16 HOW SUPPLIED/STORAGE AND HANDLING

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is supplied as white to off-white, uncoated, standard round tablet, debossed with **NXG** on one side and **CC** on the other side. Supplied in bottles of 100 tablets: NDC 0722-7184-01.

Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure.

Keep this and all medicine out of reach of children.

17 PATIENT COUNSELING INFORMATION

Overdosage: Advise patients not to increase the dose or dosing frequency of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS because serious adverse events such as respiratory depression may occur with overdosage. *[see Warnings and Precautions (5.2); Overdosage (10)]*

Concomitant Use of Alcohol and Other Central Nervous System Depressants: Advise patients to avoid the use of alcohol and other central nervous system depressants while taking CODEINE AND CHLORPHENIRAMINE MALEATE ER TABLETS because additional reduction in mental alertness may occur *[see Warnings and Precautions (5.5)]*.

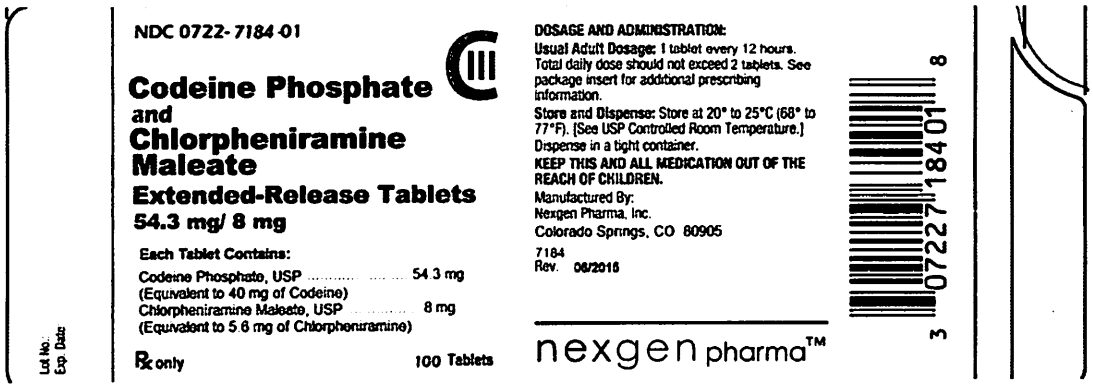
Activities Requiring Mental Alertness: Caution patients that CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. *[see Warnings and Precautions (5.5)]*

Controlled Substance Status/Potential for Abuse and Dependence: Caution patients that CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS contains codeine and can produce drug dependence. *[see Abuse and Dependence (9.2, 9.3)]*.

Manufactured by:
Nexgen Pharma, Inc.
Colorado Springs, CO 80905

(Rev. 06/2015)

Package/Label Display Panel



Patient Medication Information

PATIENT INFORMATION
CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS CIII

What is the most important information I should know about CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

- **Do not** give CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS to a child to treat pain after tonsillectomy or adenoidectomy surgery.
  - When you take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, some of it changes into morphine in your body.
  - In some children and adults this happens very quickly, and can cause you to stop breathing and cause death due to an overdose.
- Women who breastfeed should talk to their healthcare provider before taking CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS
  - When you take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, some of it changes into morphine in your body.
  - In some women, this happens very quickly. Codeine and morphine pass into your breast milk. A large amount of morphine can cause your baby to die.
- Call your healthcare provider or get emergency medical help right away if anyone taking CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, or your breastfeeding baby has any of the symptoms listed below:
  - increased sleepiness
  - confusion
  - difficulty breathing
  - shallow breathing
  - limpness
  - your baby has difficulty breastfeeding
- Keep CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, get emergency help right away.
- CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS can cause serious side effects, including death.
- Take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS exactly as prescribed by your healthcare provider. If you take the wrong dose of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, you could overdose and die.
- It is especially important when you take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS that you know exactly what dose to take.

What is CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is a prescription medicine used to treat cough and upper respiratory symptoms you can have with allergies or a common cold. CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is for adults 18 years and older. CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS contains 2 medicines, codeine and chlorpheniramine. Codeine is a narcotic cough suppressant. Chlorpheniramine is an antihistamine.

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is a controlled substance (CIII) because it contains codeine that can be a target for people who abuse prescription medicines or street drugs. Keep your CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS in a safe place to protect it from theft. Never give your CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS to anyone else even if they have the same symptoms you have. It may harm them or even cause death. Selling or giving away this medicine is against the law.

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is not for children under 18 years of age. It is not known if CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is safe and effective in children.

Who should not take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

Do not give CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS to a child to treat pain after tonsillectomy or adenoidectomy surgery.

Do not take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS if you are allergic to any of the ingredients in CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. See the end of this leaflet for a complete list of ingredients in CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS.

What should I tell my healthcare provider before taking CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

Before you take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, tell your healthcare provider if you:

- have a drug dependence
- have lung or breathing problems
- have had a head injury
- have pain in your stomach (abdomen)
- have prostate problems
- have problems with your urinary tract (urethral stricture)
- plan to have surgery
- abuse alcohol
- have kidney or liver problems
- have thyroid problems, such as hypothyroidism
- are pregnant or plan to become pregnant. It is not known if CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS will harm your unborn baby. You and your healthcare provider should decide if you should take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS while you are pregnant.
- are breastfeeding or plan to breastfeed. CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS can pass into your milk and may harm your baby. You and your healthcare provider should discuss whether you should take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS or breastfeed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Using CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS with certain other medicines may affect each other. Using CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS with other medicines can cause serious side effects.

Especially tell your healthcare provider if you:

- take pain medicines such as narcotics
- take cold or allergy medicines that contain antihistamines or cough suppressants
- take medicines for mental illness (anti-psychotics, anti-anxiety)
- drink alcohol
- take medicines for depression including monoamine oxidase inhibitors (MAOIs)
- take medicines for stomach or intestine problems

How should I take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

- Take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS exactly as your healthcare provider tells you.
- Do not take more than 2 CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS in 24 hours.
- CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS can be taken with or without food.
- Do not mix CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS with other fluids or medicines.
- If you take too much CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid doing while taking CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

- CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS can cause you to be drowsy. Do not drive a car or use machinery while you take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS until you know how it affects you.
- Do not drink alcohol while taking CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS may cause serious side effects, including:

- **See "What is the most important information I should know about CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS"**
- **decreased breathing** (respiratory depression) which can lead to death. Call your healthcare provider or get emergency treatment right away if you have excessive sleepiness, shallow or slow breathing, or confusion.
- **physical dependence or abuse. Take CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS exactly as your healthcare provider tells you to take it.** Stopping CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS suddenly could cause withdrawal symptoms.
- **bowel problems** including constipation or stomach pain.

The most common side effects of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS are: nausea, vomiting, blurred vision, double vision, confusion, dizziness, depression, excessive sleepiness, headache, feeling faint, light-headedness, general feeling of discomfort or illness, excitability, nervousness, agitation, and restlessness.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS?

- Store CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS in a safe place between 20°C to 25°C (68°F to 77°F).
- Keep CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS in a tightly closed container out of the light.
- Safely throw away medicine that is out of date or no longer needed.
- Keep CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS and all medicines out of the reach of children.

General information about CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS for a condition for which it was not prescribed. Do not give CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS to other people, even if they have the same condition. It may harm them and it is against the law.

This Patient Information Leaflet summarizes the most important information about CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS that is written for healthcare professionals.

Other ingredients in CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS

Hypromellose (hydroxypropyl methylcellulose), lactose monohydrate, cellulose microcrystalline, polysorbate 80, magnesium stearate, and colloidal silicon dioxide.

For more information about CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS call Nexgen Pharma, Inc., at 888-710-0006 or go to www.nexgenpharma.com