

Attachment F

**Labeling for *Tussionex® Pennkinetic®*
(*hydrocodone polisterex and
chlorpheniramine polistirex*) *Extended
Release Suspension***

and

***Codeprex™ Pennkinetic®* (*codeine
polisterex and chlorpheniramine
polistirex*) *Extended Release
Suspension***

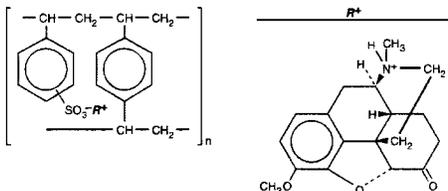
Tussionex® 
Pennkinetic®

(hydrocodone polistirex and chlorpheniramine polistirex)
Extended-Release Suspension

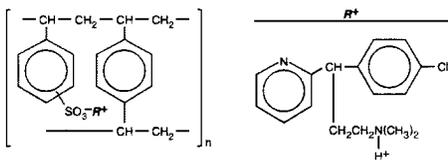
Rx Only
LR242A
Rev. 12/02

DESCRIPTION: Each teaspoonful (5 mL) of TUSSIONEX Pennkinetic Extended-Release Suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. TUSSIONEX Pennkinetic Extended-Release Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. TUSSIONEX Pennkinetic Extended-Release Suspension is for oral use only.

Hydrocodone Polistirex: sulfonated styrene-divinylbenzene copolymer complex with 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one.



Chlorpheniramine Polistirex: sulfonated styrene-divinylbenzene copolymer complex with 2-[p-chloro- α -(2-(dimethylamino)ethyl)-benzyl]pyridine.



Inactive Ingredients: Ascorbic acid, D&C Yellow No. 10, ethylcellulose, FD&C Yellow No. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propylparaben, purified water, sucrose, vegetable oil, xanthan gum.

CLINICAL PHARMACOLOGY: Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, physical and psychological dependence.

Chlorpheniramine is an antihistamine drug (H₁ receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone release from TUSSIONEX Pennkinetic Extended-Release Suspension is controlled by the Pennkinetic System, an extended-release drug delivery system which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system.

Following multiple dosing with TUSSIONEX Pennkinetic Extended-Release Suspension, hydrocodone mean (S.D.) peak plasma concentrations of 22.8 (5.9) ng/mL occurred at 3.4 hours. Chlorpheniramine mean (S.D.) peak plasma concentrations of 58.4 (14.7) ng/mL occurred at 6.3 hours following multiple dosing. Peak plasma levels obtained with an immediate-release syrup occurred at approximately 1.5 hours for hydrocodone and 2.8 hours for chlorpheniramine. The plasma half-lives of hydrocodone and chlorpheniramine have been reported to be approximately 4 and 16 hours, respectively.

INDICATIONS AND USAGE: TUSSIONEX Pennkinetic Extended-Release Suspension is indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold.

CONTRAINDICATIONS: Known allergy or sensitivity to hydrocodone or chlorpheniramine.

WARNINGS: Respiratory Depression: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. Caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively and in patients with pulmonary disease or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see OVER-DOSAGE).

Head injury and increased intracranial Pressure: The respiratory depressant effects of narcotics 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, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease: Chronic use of narcotics may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Pediatric Use: In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Benefit to risk ratio should be carefully considered especially in pediatric patients with respiratory embarrassment (e.g., croup) (see PRECAUTIONS).

PRECAUTIONS: General: Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma or prostatic hypertrophy.

Special Risk Patients: As with any narcotic agent, TUSSIONEX Pennkinetic Extended-Release Suspension should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, 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.

Information for Patients: As with all narcotics, TUSSIONEX Pennkinetic Extended-Release Suspension 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; patients should be cautioned accordingly. TUSSIONEX Pennkinetic Extended-Release Suspension must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity. Keep out of the reach of children.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when TUSSIONEX Pennkinetic Extended-Release Suspension is used postoperatively, and in patients with pulmonary disease.

Drug Interactions: Patients receiving narcotics, antihistaminics, antipsychotics, anti-anxiety agents or other CNS depressants (including alcohol) concomitantly with TUSSIONEX Pennkinetic Extended-Release Suspension may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and reproductive studies have not been conducted with TUSSIONEX Pennkinetic® (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension.

Pregnancy: Teratogenic Effects - Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. TUSSIONEX Pennkinetic Extended-Release Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: 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.

Labor and Delivery: As with all narcotics, administration of TUSSIONEX Pennkinetic Extended-Release Suspension to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TUSSIONEX Pennkinetic Extended-Release Suspension, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of TUSSIONEX Pennkinetic Extended-Release Suspension in pediatric patients under six have not been established (see WARNINGS).

Geriatric Use: Clinical studies of TUSSIONEX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 of other drug therapy.

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

ADVERSE REACTIONS: Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, euphoria, dizziness, psychic dependence, mood changes.

Dermatologic System: Rash, pruritus.

Gastrointestinal System: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of TUSSIONEX Pennkinetic Extended-Release Suspension may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesicle sphincters and urinary retention have been reported with opiates.

Respiratory Depression: TUSSIONEX Pennkinetic Extended-Release Suspension may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVER-DOSAGE).

Respiratory System: Dryness of the pharynx, occasional tightness of the chest.

DRUG ABUSE AND DEPENDENCE: TUSSIONEX Pennkinetic Extended-Release Suspension is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, TUSSIONEX Pennkinetic Extended-Release Suspension should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when TUSSIONEX Pennkinetic Extended-Release Suspension is used for a short time for the treatment of cough. 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 narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy.

OVERDOSAGE: Signs and Symptoms: Serious overdose with hydrocodone 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. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdose apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdose may vary from central nervous system depression to stimulation.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdose or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone in this formulation 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. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION: Shake well before using.

Adults: 1 teaspoonful (5 mL) every 12 hours;
do not exceed 2 teaspoonfuls in 24 hours.

Children 6-12: 1/2 teaspoonful every 12 hours;
do not exceed 1 teaspoonful in 24 hours.

Not recommended for children under 6 years of age (see PRECAUTIONS).

HOW SUPPLIED: TUSSIONEX Pennkinetic (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension is a gold-colored suspension.

NDC 53014-548-67 473 mL bottle

Shake well. Dispense in a well-closed container. Store at 59°-86°F (15°-30°C).

CELLTECH

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Rochester, NY 14623 USA

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Tussionex® Pennkinetic® Extended-Release Suspension: US Patent No. 4,762,709.2

Rev. 12/02
LR242A

Codeprex™
Pennkinetic®



(codeine polistirex and chlorpheniramine polistirex)
Extended-Release Suspension

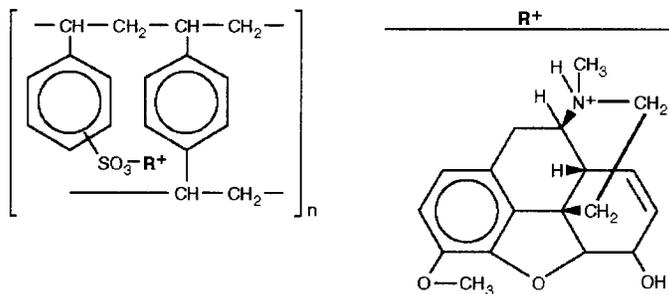
Rx Only

LR428

Rev. 6/04

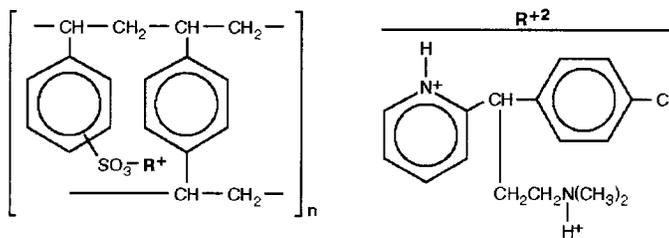
DESCRIPTION: Codeprex Extended-Release Suspension is a pink to purple-pink colored, cherry-cream flavored suspension. Each teaspoonful (5 mL) of Codeprex Extended-Release Suspension contains codeine polistirex equivalent to 20 mg of codeine and chlorpheniramine polistirex equivalent to 4 mg of chlorpheniramine maleate and excipients. These excipients include: Citric acid (anhydrous), D&C Red No. 33, edetate disodium, ethylcellulose, flavor, glycerin, methylparaben, microcrystalline cellulose, carboxymethylcellulose sodium, polyethylene glycol 3350, polysorbate 80, propylparaben, propylene glycol, purified water, sodium hydroxide, sodium polystyrene sulfonate, sucrose, vegetable oil, and xanthan gum. Codeine is an opiate antitussive. Chlorpheniramine is an antihistamine. Codeprex is for oral use only.

Chemically, codeine is (5 α ,6 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol. Its empirical formula is C₁₈H₂₁NO₃, and its molecular weight is 299.36. Codeine polistirex is the sulfonated styrene-divinylbenzene copolymer complex with codeine. Its structural formula is:



Chemically, chlorpheniramine is γ -(4-chlorophenyl)-*N,N*-dimethyl-2-pyridinepropanamine. Its empirical formula is C₁₆H₁₉ClN₂, and its molecular weight is 274.80 (free base).

Chlorpheniramine polistirex is the sulfonated styrene-divinylbenzene copolymer complex with chlorpheniramine. Its structural formula is:



CLINICAL PHARMACOLOGY: Pharmacodynamics: Codeine: The precise mechanism of action of codeine and other opiates is not known but it is believed to act in the medulla with depression of the cough center and to a lesser degree the respiratory center.

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.

Pharmacokinetics: The bioavailability of Codeprex has been assessed in single- and multiple-dose crossover studies in healthy adults. In a single-dose study, pharmacokinetic parameters for Codeprex were evaluated in 20 fasting subjects and compared to two doses of an immediate-release reference solution containing 20 mg codeine and 4 mg chlorpheniramine maleate. In a separate study, single doses of Codeprex were administered to 36 subjects, under both fed and fasted conditions. In a multi-dose study, the steady state pharmacokinetic parameters of codeine and chlorpheniramine were compared in 26 subjects who received Codeprex administered twice daily and an immediate-release reference solution administered four times daily for one week.

Absorption: In two single dose studies with Codeprex in fasting, healthy volunteers, codeine mean (S.D.) peak plasma concentrations were 53.8 (13.4) ng/mL and 61.7 (18.5) ng/mL. Chlorpheniramine mean (S.D.) peak plasma concentrations were 7.9 (1.6) ng/mL and 7.4 (1.6) ng/mL. Peak plasma codeine levels were reached approximately 2.5 to 3 hours following dosing. Peak plasma chlorpheniramine levels were reached approximately 6.5 to 7 hours following dosing. Peak plasma concentrations of codeine and chlorpheniramine were reached approximately 2.7 and 9 hours respectively after dosing with the immediate-release reference solution.

Following multiple dosing with Codeprex, codeine mean (S.D.) peak plasma concentrations of 100.5 (26.8) ng/mL were reached at approximately 2 hours. Chlorpheniramine mean (S.D.) peak concentrations of 35.8 (10.0) ng/mL were reached approximately 3 hours following multiple dosing. Peak plasma concentrations of codeine and chlorpheniramine were reached approximately 1 and 3 hours respectively after dosing with the immediate-release reference solution.

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.

Food Effects: The bioavailability of Codeprex Extended-Release Suspension was not affected when administered after a high fat meal. In a two-way crossover study, pharmacokinetic parameters were evaluated in 36 healthy subjects and no differences between fed and fasted groups were observed for either C_{max} or AUC for either codeine or chlorpheniramine. A statistically significant increase in T_{max} for chlorpheniramine from 6.3 hours to 9.1 hours was observed after a high fat meal; however this increase is unlikely to be clinically important.

Metabolism: Codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide, and to a minor extent via *O*-demethylation to morphine (approximately 10% of administered dose) and via *N*-demethylation to norcodeine (approximately 10% of administered dose). Cytochrome P-450 2D6 is the major enzyme mediating *O*-demethylation of codeine to morphine. Norcodeine formation is predominately catalyzed by cytochrome P-450 3A4 mediated *N*-demethylation. Norcodeine and morphine are further metabolized by conjugation with glucuronic acid. These metabolites and their conjugates are pharmacologically active. Whether codeine-6-glucuronide has pharmacological activity is unknown, but activity similar to codeine itself is expected.

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-lives of codeine have been reported to be approximately 3 hours.

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-lives for chlorpheniramine have been reported to range from approximately 2 to 43 hours in adults and 5 to 16 hours in children.

INDICATIONS AND USAGE: Codeprex is indicated for the temporary relief of cough, as may occur with the common cold or inhaled irritants, and for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy watery eyes due to hay fever, other upper respiratory allergies, or allergic rhinitis.

CONTRAINDICATIONS: Codeprex should not be administered to persons known to be hypersensitive to codeine, chlorpheniramine, or other components of the product. Persons known to be hypersensitive to certain other opioids may exhibit cross-sensitivity to codeine.

WARNINGS: Respiratory Depression: Codeprex is not recommended for use in pediatric patients under 6 years of age. Pediatric patients under 2 years of age may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death (see PRECAUTIONS, Pediatric Use).

As with other opioids, codeine produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Codeine affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. Caution should be exercised when Codeprex is used postoperatively, in patients with pulmonary disease or shortness of breath, or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see OVERDOSAGE).

Head Injury and Increased Intracranial Pressure: Respiratory depressant 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 which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: Administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease: Chronic use of opioids may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Respiratory Conditions: Codeprex should be used with caution in patients with persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or with cough accompanied by excessive phlegm. In patients with asthma or pulmonary emphysema, the indiscriminate use of antitussives may precipitate respiratory insufficiency due to increased viscosity of bronchial secretions and suppression of the cough reflex. In addition, the anticholinergic activity of antihistamines might reduce the volume and cause thickening of bronchial secretions and thus result in obstruction of the respiratory passages. Benefit to risk ratio should be carefully considered especially in pediatric patients with respiratory embarrassment (e.g., croup). (See PRECAUTIONS.)

PRECAUTIONS: General: Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma or prostatic hypertrophy. Codeine may cause or aggravate constipation.

Special Risk Patients: As with other opioids, Codeprex should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, 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.

Cough Reflex: Codeine suppresses the cough reflex; as with other opioids, caution should be exercised when Codeprex is used postoperatively, and in patients with pulmonary disease.

Information for Patients: Patients should be advised that Codeprex 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; patients should be cautioned accordingly.

Codeprex must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity.

Antihistamines such as chlorpheniramine may also cause excitability, especially in children. Keep out of the reach of children. Careful parental education should be provided about the appropriate use and side effects of cough-cold medications, particularly in younger children. Patients should be advised that recommended dosages should not be exceeded.

Drug Interactions: Anticholinergics: Additive adverse effects resulting from cholinergic blockade (e.g., xerostomia, blurred vision, constipation) may occur when anticholinergic drugs are administered with chlorpheniramine. Codeine and chlorpheniramine should be administered cautiously to persons receiving other anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects.

Antidepressants: Use of MAO inhibitors or tricyclic antidepressants with codeine may increase the effect of either the antidepressant or codeine. MAO inhibitors may prolong and intensify the anticholinergic and sedative effects of antihistamines such as chlorpheniramine. Codeine and chlorpheniramine should be administered cautiously and in reduced dosage to persons receiving MAO inhibitors or tricyclic antidepressants in order to avoid excessive sedation, acute hypotension and excessive anticholinergic effects.

CNS Depressants: Concurrent use of opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Codeprex may result in additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Metabolic Enzymes: Codeine is metabolized to pharmacologically active metabolites by the cytochrome P-450 2D6 and 3A4 isoenzymes (see CLINICAL PHARMACOLOGY). The concurrent use of drugs that preferentially induce codeine N-demethylation (cytochrome P-450 3A4) or drugs that are strong inhibitors of codeine O-demethylation (cytochrome P-450 2D6), 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. Persons taking cytochrome P-450 enzyme inducers or inhibitors may demonstrate an altered response to codeine, therefore antitussive activity should be monitored.

Phenytoin: Chlorpheniramine may inhibit the hepatic metabolism of phenytoin. Reports in the literature suggest a possible association between the concurrent administration of chlorpheniramine and phenytoin with increased serum phenytoin levels and phenytoin toxicity. Monitoring patients for evidence of phenytoin toxicity such as ataxia, hyperreflexia, nystagmus and tremor is recommended. If the patient exhibits signs of toxicity, a serum phenytoin level should be considered and Codeprex should be discontinued immediately.

Drug-Laboratory Test Interactions: Codeprex 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although studies with Codeprex to evaluate carcinogenic, mutagenic or impairment of fertility potential have not been conducted, published data are 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 8 and 20 times, respectively, the maximum recommended daily 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 15 times the maximum recommended dose for adults and children 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.

In rats and rabbits, oral doses of chlorpheniramine maleate up to approximately 20 and 25 times the human dose on a mg/m² basis, respectively, did not impair fertility.

Pregnancy: Pregnancy Category C.

Teratogenic Effects: Although animal reproductive studies with CodeprexTM Pennkinetic[®] (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension have not been conducted, published data are available which address reproductive toxicity of the active ingredients.

Codeine: In a study in which pregnant rats were dosed throughout organogenesis, an oral dose of 120 mg/kg/day (approximately 10 times the maximum recommended daily dose for adults on a mg/m² basis) 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, oral doses up to 30 and 600 mg/kg/day, respectively (approximately 6 and 30 times, respectively, the maximum recommended daily dose for adults on a mg/m² basis), produced no adverse developmental effects.

Chlorpheniramine: In studies in which pregnant rats and rabbits were dosed throughout organogenesis, oral doses up to approximately 20 and 25 times the maximum recommended daily dose for adults on a mg/m² basis, respectively, produced no adverse developmental effects. However, when mice were dosed throughout pregnancy, an oral dose of 20 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m² basis) was embryolethal, and postnatal survival was decreased when dosing was continued after parturition. Embryolethality was also observed when male and female rats were dosed prior to mating with 10 mg/kg/day (approximately 5 times the maximum recommended daily dose for adults on a mg/m² basis).

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.

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

Non-teratogenic 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.

Labor and Delivery: As with other opioids, use of codeine during labor can produce respiratory depression in the neonate, especially if higher doses are used. If the mother receives opiates during labor, the newborn should be observed closely for signs of respiratory depression. Treatment of respiratory depression may require active resuscitation and the use of specific opioid-antagonists (e.g., naloxone).

Nursing Mothers: Caution should be exercised when Codeprex is administered to a nursing woman.

Codeine and its metabolite morphine, appear in human milk at low levels, although considerable variability exists. Low levels of free codeine and its metabolite morphine are present in neonatal plasma after exposure to breast milk containing these substances. Care should be taken to monitor the infant carefully for signs of central nervous system and respiratory depression.

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

Pediatric Use: Safety and effectiveness of Codeprex in patients under 6 years of age have not been established. Codeprex is not recommended for use in patients under 6 years of age. Patients under 2 years of age may be more susceptible to the respiratory depressant effects of codeine,

including respiratory arrest, coma, and death (see WARNINGS). Additionally, antihistamines may cause excitability in pediatric patients.

Geriatric Use: Clinical studies of Codeprex did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, sedating drugs 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.

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

ADVERSE REACTIONS: Adverse reactions listed below have been reported in the literature for codeine and chlorpheniramine and may be expected to occur with Codeprex. Also included are events which occurred during clinical pharmacokinetic studies (in a total of 147 healthy adult volunteers with either single or multiple dose exposure) with Codeprex and judged by the investigator to be related to study treatment. There are insufficient data to support a statement regarding distribution of adverse events by gender, race and age (see PRECAUTIONS: Pediatric Use and PRECAUTIONS: Geriatric Use).

Body as a Whole: Asthenia, feeling of relaxation, redness or flushing of the face, unusual tiredness or weakness.

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

Cardiovascular: Fast, slow, or pounding heartbeat, hypertension, hypotension, orthostatic hypotension, palpitation, shock-like state, syncope.

Dermatologic System: Dermatitis, excessive perspiration, urticaria, erythema, pruritus, rash.

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

Gastrointestinal: Abdominal distension, abdominal pain, acute pancreatitis, constipation, diarrhea, dry mouth, dyspepsia, epigastric distress, loss of appetite, nausea, vomiting; also observed with opioids: decreased gastric motility with increased likelihood of esophageal reflux.

Genitourinary: Dysuria, irritative bladder symptoms, urinary frequency, urinary hesitancy, urinary retention, ureteral spasm.

Nervous System: Blurred, double, or other visual disturbances; confusion; dizziness; depression; drowsiness and sedation; headache; euphoria; facial dyskinesia; false sense of well-being; feeling faint, lightheadedness, general feeling of discomfort or illness; may cause excitability, especially in children; nervousness, agitation and restlessness; minimal sedation; somnolence; also observed with antihistamine agents: insomnia, dyskinesia, irritability, tremor.

Respiratory System: Dryness of pharynx and respiratory passages, laryngismus, nasal stuffiness, wheezing or troubled breathing, respiratory depression.

Special Senses: Ears: labyrinthitis, tinnitus, vertigo; eyes: blurred vision, diplopia, hypermetropia, lacrimation increased, mydriasis, photophobia.

Other: Drug fever.

DRUG ABUSE AND DEPENDENCE: Controlled Substance: Codeprex is a controlled narcotic in Schedule III of the Controlled Substances Act (CSA).

Abuse and Dependence: Codeine must be administered under close supervision to patients with a history of drug abuse or dependence. Codeine can produce drug dependence and therefore has the potential for abuse. Dependence and tolerance may develop upon repeated administration. An opioid withdrawal syndrome, indicating the development of dependence, may appear if the drug product is administered continuously for an extended time period.

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.

OVERDOSAGE: Signs and Symptoms: Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miosis (mydriasis may occur in terminal narcosis or severe hypoxia), skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

The estimated lethal dose of codeine in adults is 7 to 14 mg/kg body weight. Ingestion of more than 5 mg/kg of codeine has caused respiratory arrest in children. Ingestion of greater than 1 mg/kg of codeine may produce symptoms in children. Infants and children may demonstrate unusual sensitivity to opioids and habituated adults may have extreme tolerance to opioids.

Manifestations of chlorpheniramine overdose 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 overdose 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.

Oral lethal doses of chlorpheniramine maleate were 130, 306 and 198 mg/kg in mice, rats and guinea pigs, respectively (approximately 35, 170 and 150 times, respectively, the maximum recommended daily dose for adults and children on a mg/m² basis). 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: Treatment of overdose should provide symptomatic and supportive care. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation as necessary. Oxygen, intravenous fluid, vasopressors, and other supportive measures should be employed as indicated. Induction of emesis is not recommended because of the potential for CNS depression and seizures. Gastric lavage may be useful in removing unabsorbed drug. 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 narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression resulting from overdose 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 in this formulation 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.

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 (see CLINICAL PHARMACOLOGY), 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.

DOSAGE AND ADMINISTRATION: Shake well before using.

Adults and adolescents, ages 12 and older: Two teaspoonfuls (10 mL) every 12 hours; do not exceed four teaspoonfuls in 24 hours.

Children ages 6 to under 12: One teaspoonful (5 mL) every 12 hours; do not exceed two teaspoonfuls in 24 hours.

Not recommended for patients under 6 years of age (see WARNINGS and PRECAUTIONS).

HOW SUPPLIED: Codeprex (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension is a pink to purple-pink colored, cherry-cream flavored suspension, available in an amber colored plastic bottle for oral use only.

NDC 53014-826-67 473 mL bottle

Shake well. Dispense in a well-closed container, and protect from light. Store at controlled room temperature not to exceed 25°C (77°F). Keep out of the reach of children.



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