LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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March 7, 2003

OVERNIGHT COURIER 3/7/03

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules (equivalent to 10 mg Hydrocodone Bitartrate and equivalent to 8 mg Chlorpheniramine Maleate) and Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules (equivalent to 5 mg Hydrocodone Bitartrate and equivalent to 4 mg Chlorpheniramine Maleate) are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules (equivalent to 10 mg Hydrocodone Bitartrate and equivalent to 8 mg Chlorpheniramine Maleate) and Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules (equivalent to 5 mg Hydrocodone Bitartrate and equivalent to 4 mg Chlorpheniramine Maleate) are suitable for submission as an ANDA. The reference listed drug product upon which this petition is based is TUSSIONEX (Hydrocodone Polistirex and Chlorpheniramine Polistirex (equivalent to 10 mg / 5 mL Hydrocodone bitartrate and 8 mg / 5 mL Chlorpheniramine Maleate)) Extended-Release Suspension. TUSSIONEX is approved under NDA 19-111 and the NDA is held by Celltech Pharmaceuticals. A copy of the appropriate page (3-78) of the *Approved Drug Products with Therapeutic Equivalence Evaluations* 22nd edition that lists the approval is provided in Attachment 1. The petitioner thus seeks a change in the dosage form (from an extended-release suspension to an extended-release capsule) from that of the reference listed drug and a change in strength [from 10 mg / 8 mg equivalents of Hydrocodone Bitartrate / Chlorpheniramine Maleate per dosage unit (5 mL) to 5 mg / 4 mg equivalents of Hydrocodone Bitartrate / Chlorpheniramine Maleate per capsule (for the half-strength capsule]).

03P-0091

CP1

B. Statement of Grounds

The reference-listed drug (RLD) product is currently available in an extended-release suspension of which each teaspoonful (5 mL) of TUSSIONEX contains Hydrocodone Polistirex equivalent to 10 mg of Hydrocodone Bitartrate and Chlorpheniramine Polistirex equivalent to 8 mg of Chlorpheniramine Maleate. The proposed drug product, with the exception of the dosage form and directions for administration (suspension vs. capsule) is consistent with the currently approved RLD product's labeling and will provide an alternate dosage form that may prove to be more easily administered to patients that prefer a capsule vs. a suspension. In addition, the availability of a capsule dosage form will eliminate any problems associated with convenience of dosing (need to have an appropriate measuring device to provide the required dose), and will also eliminate any issue that may be associated with the taste of the suspension. The petition is thus seeking a change in the dosage form (from extended-release suspension to extended-release capsule) and a change in strength (to include a one-half strength capsule to facilitate pediatric dosing as outlined in the labeling of the approved drug product) from that of the RLD.

The RLD is indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold according to the approved labeling for the RLD. The dosage and administration section of the labeling reads as follows:

> 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 teaspoon every 12 hours;
> **do not exceed 1 teaspoonful in 24 hours.**
>
> Not recommended for children under 6 years of age (see PRECAUTIONS).

The petitioner is seeking the requested change in dosage form and strength from that of the RLD to provide the physician greater flexibility in administering an alternate dosage form that is consistent with doses, indications and uses as described in the approved RLD's labeling. The new dosage form will improve patient convenience, compliance and make it easier to administer the correct dosage amounts, and will eliminate the need for a measuring device for patient dosing. The one-half strength capsule will permit dosing in pediatric patients ages 6-12 years consistent with the approved labeling of the reference-listed drug product.

Copies of the labeling of the reference-listed drug product upon which this petition is based and draft labeling for the proposed product are included in Attachments 2 and 3, respectively. The proposed labeling is the same as the approved RLD labeling with the exception of changes allowed because the manufacturer of the generic product differs from that of the RLD and those changes that would be necessitated by the change in dosage form and strength requested in this petition. There are no changes in the doses recommended, the indications, or conditions of use sections of the labeling.

Therefore, the petitioner requests that the Commissioner find that a change in dosage form from an extended-release suspension to an extended-release capsule and a change in strength to include a one-half strength extended-release capsule for this proposed product raises no questions of safety or effectiveness, and the Agency should, therefore, approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert W. Pollock
Vice President

RWP/pk

Attachments: *Approved Drug Products with Therapeutic Equivalence Evaluations* 22nd Edition, page 3-78
Tussionex Approved Labeling
Draft Labeling for the Proposed Product Subject of this Petition

cc: Gregg Davis (Office of Generic Drugs)
Martin Shimer (Office of Generic Drugs)

M03P3066

ATTACHMENT 1

CHLORPHENIRAMINE MALEATE

TABLET; ORAL

CHLORPHENIRAMINE MALEATE

AA	+ ICN	4MG	N80598 001	
AA	MARSHALL PHARMA	4MG	N83286 001	
AA	PHOENIX LABS NY	4MG	N85522 001	
AA	SUPERPHARM	4MG	N87747 001	APR 20, 1982
AA	TABLICAPS	4MG	N83394 001	

CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

SUSPENSION, EXTENDED RELEASE; ORAL

TUSSIONEX

	+ CELLTECH PHARMS	EQ 8MG MALEATE/5ML; EQ 10MG BITARTRATE/5ML	N19111 001	DEC 31, 1987

CHLORPROMAZINE

SUPPOSITORY; RECTAL

THORAZINE

	+ GLAXOSMITHKLINE	25MG	N09149 024	
	+	100MG	N09149 033	

CHLORPROMAZINE HYDROCHLORIDE

CAPSULE, EXTENDED RELEASE; ORAL

THORAZINE

	+ GLAXOSMITHKLINE	30MG	N11120 016	
	+	75MG	N11120 017	
	+	150MG	N11120 018	
	+	200MG	N11120 019	
	+	300MG	N11120 020	

CONCENTRATE; ORAL

CHLORPROMAZINE HCL

AA	ALPHARMA	100MG/ML	N86863 001	
AA	PHARM ASSOC	30MG/ML	N40231 001	DEC 30, 1999
AA		100MG/ML	N40224 001	JAN 26, 1999

CHLORPROMAZINE HCL INTENSOL

AA	ROXANE	30MG/ML	N88157 001	APR 27, 1983

CHLORPROMAZINE HYDROCHLORIDE

CONCENTRATE; ORAL

CHLORPROMAZINE HCL INTENSOL

AA	ROXANE	100MG/ML	N88158 001	APR 27, 1983

SONAZINE

AA	GENEVA PHARMS	30MG/ML	N80983 004	
AA		100MG/ML	N80983 005	

THORAZINE

AA	+ GLAXOSMITHKLINE	30MG/ML	N09149 032	
AA	+	100MG/ML	N09149 043	

INJECTABLE; INJECTION

CHLORPROMAZINE HCL

AP	ELKINS SINN PHARM	25MG/ML	N83329 001	

THORAZINE

AP	+ GLAXOSMITHKLINE	25MG/ML	N09149 011	

SYRUP; ORAL

SONAZINE

AA	GENEVA PHARMS	10MG/5ML	N83040 001	

THORAZINE

AA	+ GLAXOSMITHKLINE	10MG/5ML	N09149 022	

TABLET; ORAL

CHLORPROMAZINE HCL

BP	GENEVA PHARMS	10MG	N80439 001	
BP		25MG	N80439 002	
BP		50MG	N80439 003	
BP		100MG	N80439 004	
BP		200MG	N80439 005	
BP	LEDERLE	10MG	N84803 001	
BP	USL PHARMA	10MG	N83386 001	
BP		25MG	N84112 001	
BP		50MG	N84113 001	
BP		100MG	N84114 001	
BP		200MG	N84115 001	

THORAZINE

BP	+ GLAXOSMITHKLINE	10MG	N09149 002	
BP		25MG	N09149 007	
BP		50MG	N09149 013	
BP	+	100MG	N09149 018	
BP		200MG	N09149 020	

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 2

Tussionex® (III)

LR226B
Rev 6/98

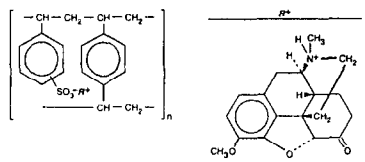
Pennkinetic®

(hydrocodone polistirex and chlorpheniramine polistirex)

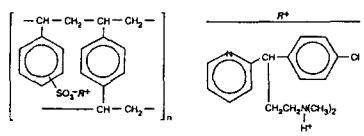
Extended-Release Suspension

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 4,5α-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 (H_1 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 6 (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 OVERDOSAGE)

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, antianxiety 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

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 OVERDOSAGE)

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 overdosage 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 overdosage apnea, circulatory collapse, cardiac arrest and death may occur The manifestations of chlorpheniramine overdosage 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 overdosage 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)

℞ Only

Medeva

Medeva Pharmaceuticals, Inc.
Rochester, NY 14623 USA

Rev 6/98
LR226B

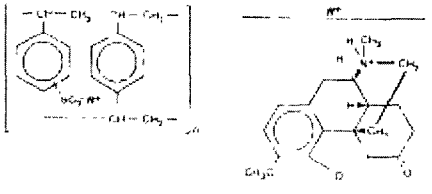
ATTACHMENT 3

CIII

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules
Rx only

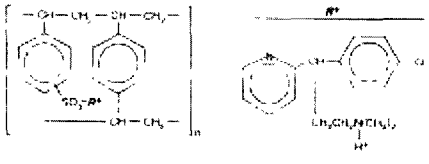
DESCRIPTION: Each full strength Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsule contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. Each half strength Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsule contains hydrocodone polistirex equivalent to 5 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 4 mg of chlorpheniramine maleate. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules provide up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules are for oral use only.

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



Polistirex Hydrocodone

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



Polistirex Chlorpheniramine

Inactive Ingredients: (to be listed upon submission).

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 (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone and Chlorpheniramine release from Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules is controlled by use of an ion-exchange polymer matrix.

Following multiple dosing with Hydrocodone Polistirex and Chlorpheniramine Polistirex 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: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules are 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, Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules produce 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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules are 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 OVERDOSAGE).

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, Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules 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, Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules 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. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules 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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules are used postoperatively, and in patients with pulmonary disease.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules 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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules.

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. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules 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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules 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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules, 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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules in pediatric patients under six have not been established.

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 Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules may produce constipation.

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

Respiratory Depression: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

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

DRUG ABUSE AND DEPENDENCE: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules are Schedule III narcotics. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsules are 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 overdosage 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 sometime bradycardia and hypotension. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdosage 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 overdosage 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:

Adults: One full strength Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsule (hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate) every 12 hours;
do not exceed 2 capsules in 24 hours.

Children 6-12: One half-strength Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Capsule (hydrocodone polistirex equivalent to 5 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 4 mg of chlorpheniramine maleate).
do not exceed 2-half-strength capsules in 24 hours.

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

HOW SUPPLIED:

Full strength

Hydrocodone Polistirex/ Chlorpheniramine Polistirex (eq. to Hydrocodone Bitartrate 10 mg/Chlorpheniramine Maleate 8 mg) NDC XXXX-XXXX-XX

Half-strength
Hydrocodone Polistirex/ Chlorpheniramine Polistirex (eq. to Hydrocodone Bitartrate 5 mg/Chlorpheniramine Maleate 4 mg) NDC XXXX-XXXX-XX

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