CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-111 /S011

Trade Name: Tussionex Pennkinetic

Generic Name: hydrocodone polistirex/chlorpheniramine pilistirex

Sponsor: Celltech Pharmaceuticals, Inc

Approval Date: November 12, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-111 /S011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-111 /S011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-111/S-011

Celltech Pharmaceuticals, Inc
755 Jefferson Road
P.O. Box 31710
Rochester, NY 14603-1710

Attention: Cheryl A. Rini, R.N.
Senior Manager, Regulatory Affairs

Dear Ms. Rini:

Please refer to your supplemental new drug application dated May 9, 2003, received May 12, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tussionex Pennkinetic (hydrocodone polistirex/ chlorpheniramine pilistirex).

This "Changes Being Effected" supplemental new drug application provides the addition of a Geriatric Use subsection to the Precautions section of the package insert and the addition of the phrase "(See Warning)" in the Pediatric Use subsection of the Precautions section of the Package insert.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on May 9, 2003.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ladan Jafari , Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
11/12/03 09:42:41 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-111 /S011

LABELING

Current Labeling (LR242)

Revised Labeling (LR242A)

Tussionex®

Pennkinetic®

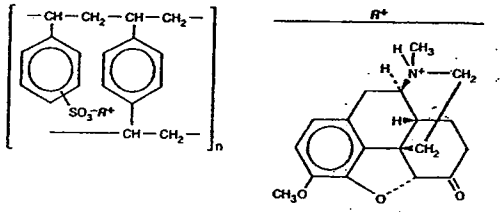
(hydrocodone polistirex and chlorpheniramine polistirex)

Extended-Release Suspension

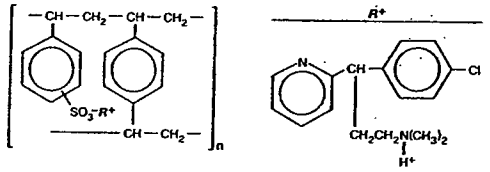
℞ Only
LR242
Rev. 7/01

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 22.8 (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.

Tussionex®

Pennkinetic®

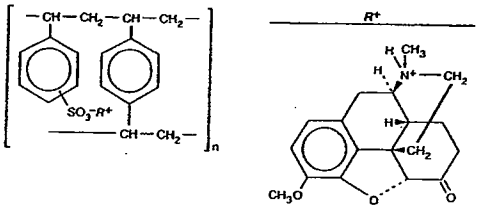
(hydrocodone polistirex and chlorpheniramine polistirex)

Extended-Release Suspension

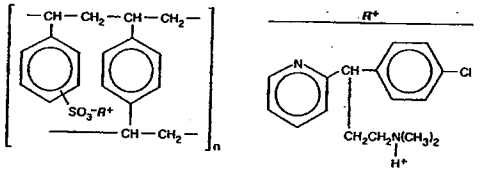
℞ Only
LR242A
Rev. 12/02

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 4,5α-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.

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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.

Current Labeling (LR242)

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.

Revised Labeling (LR242A)

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).

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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 or 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.

Current Labeling (LR242)

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).

CELLTECH

Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA

Rev. 7/01
LR242

Revised Labeling (LR242A)

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.

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CELLTECH

Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA

Tussionex® Pennkinetic® Extended-Release Suspension: US Patent No. 4,762,709.2
Rev. 12/02
LR242A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-111 /S011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Project Manager Labeling Review

NDA 19-111/S-011

DRUG: Tussionex Pennkinetic (hydrocodone polistirex/ chlorpheniramine pilistirex)

SPONSOR: Celltech Pharmacauticals, Inc.

SUBMISSION DATED: May 9, 2003 RECEIVED: May 12, 2003

This changes being effected supplemental application provides for the addition of a Geriatric Use subsection to the Precautions section of the package insert and the addition of the phrase "(See Warning)" in the Pediatric Use subsection of the Precautions section of the package insert.

Celltech submitted information supporting the addition of the Geriatric Use subsection in accordance with 21 CFR sections 201.57(f)(10)(ii)(A) and 201.57(f)(10)(iii)(B). No data is needed for the addition of "(See Warning)" to the Pediatric subsection.

I compared the labeling dated May 9, 2003, to the last approved labeling and there are no changes other than those requested by this supplement. This supplement should be approved.

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandra Barnes
11/10/03 04:43:13 PM
CSO

Peter Starke
11/10/03 05:08:36 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-111/S-011

CBE-30/CBE-0 SUPPLEMENT

Celltech Pharmaceuticals, Inc.
755 Jefferson Road
P. O. Box 31710
Rochester, NY 14603-1710

Attention: Cheryl A. Rini, R.N.
Senior Manager, Regulatory Affairs

Dear Ms. Rini:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tussionex Pennkinetic (hydrocodone bitartrate/chlorpheniramine polistirex) Extended Release Suspension

NDA Number: 19-111

Supplement number: 011

Date of supplement: May 9, 2003

Date of receipt: May 12, 2003

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes to revise the labeling for Tussionex Extended Release Suspension to include a Geriatric Use subsection in the Precautions section of the package insert.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Pulmonary & Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary & Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ladan Jafari
5/19/03 03:34:59 PM
Signed for Sandy Barnes.

CELLTECH

NDA NO. 19-111 REF NO. SIR-011
NDA SUPPL FOR Labeling

May 9, 2003

Badrul Chowdhury, M.D., Acting Director
Division of Pulmonary & Allergy Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

RECEIVED
MAY 12 2003
FDR/CDER

RE: NDA 19-111
Tussionex® Pennkinetic® (hydrocodone polistirex/chlorpheniramine politistirex)
Extended-Release Suspension

Special Supplement – Changes Being Effected
Geriatric Labeling Supplement

Dear Dr. Chowdhury:

Reference is made to the new drug application cited above, which was approved on December 31, 1987. In accordance with 21 CFR §314.70(c)(2)(i), Celltech hereby submits a "Special Supplement – Changes Being Effected" to revise the labeling for Tussionex® Extended-Release Suspension to include a Geriatric Use subsection in the Precautions section of the package circular.

In accordance with 21 CFR §201.57(f)(10)(ii)(A) and §201.57(f)(10)(iii)(B), the following text has been added as a "Geriatric Use" subsection in the Precautions section of the package circular:

> **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 or 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.

Celltech Pharmaceuticals, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31710 Rochester, NY 14603-1710
Tel: (585) 274-5346 Fax: (585) 272-3952 E-Mail: cheryl.rini@celltechgroup.com

This labeling revision is being submitted as a "Special Supplement – Changes Being Effected" in accordance with the FDA's Guidance for Industry, "Content and Format for Geriatric Labeling (October 2001)" and the Final Rule published in the *Federal Register* on August 27, 1997 (Vol. 62, No. 166, p. 45316) which states that the agency will not require prior approval of labeling changes for drug products under §201.57(f)(10)(ii)(A) where insufficient data exist to determine whether the responses of geriatric patients to a drug are different from the responses of younger patients. This was discussed and confirmed with Ladan Jafari, Project Manager, Division of Pulmonary & Allergy Drug Products on December 2, 2002.

Details of the data to support Geriatric Use labeling are provided in Section 2 of this submission.

As an additional labeling change in accordance with 21 CFR §314.70(c)(2)(i), "(see WARNINGS)" has been added to the end of the Pediatric Use subsection in the Precautions section as a cross reference to pediatric use information in the Warnings section.

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

Twelve (12) copies of final printed labeling (package circular LR242A) incorporating these revisions are enclosed in the archival copy of this submission. (Ten of these copies are individually mounted on heavy weight paper.) To facilitate review, a copy of this labeling is also enclosed with the added text in the Pediatric Use and Geriatric Use subsections highlighted compared to the current labeling for Tussionex. Celltech plans to implement this labeling on May 17, 2003, with package circular LR242A being used in product production and packaging after this date.

Please note that the active moieties in Tussionex®, hydrocodone and chlorpheniramine, were first approved as new molecular entities (NME) as follows:

- Hydrocodone – First approved as a combination drug of hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg per tablet under NDA 5-213 on March 23, 1943 (DuPont Pharmaceuticals).

- Chlorpheniramine – First approved as a syrup, 2 mg/5mL under NDA 6-921 filed by Schering on May 8, 1950. The combination product of phenylpropanolamine 20 mg and chlorpheniramine 4 mg sustained action capsule was approved on

Therefore, in accordance with the implementation schedule in the FDA's guidance for industry, "Content and Format for Geriatric Labeling (October 2001)," the date for submitting Geriatric Labeling for this drug product with an NME first approved prior to 1963, is by August 27, 2003. Please also note that this submission does not contain clinical data subject to user fees.

If you have any questions regarding this submission, please contact either Michele Bartlett, Director, Regulatory Affairs at (585) 274-5547 or the undersigned at (585) 274-5346.

Sincerely,

Cheryl A. Rini

Cheryl A. Rini, R.N.
Senior Manager, Regulatory Affairs

Cc: Ladan Jafari (cover letter only)
Regulatory Project Manager
Division of Pulmonary & Allergy Drug Products (HFD-570)

2. Labeling

The labeling is updated as follows:

Pediatric Use:

In accordance with 21 CFR §314.70(c)(2)(i), "(see WARNINGS)" has been added to the end of the Pediatric Use subsection in the Precautions section as a cross reference to pediatric use information in the Warnings section.

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

Geriatric Use:

In accordance with 21 CFR §201.57(f)(10)(ii)(A) and §201.57(f)(10)(iii)(B), the following text has been added as a "Geriatric Use" subsection in the Precautions section of the package circular:

> **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 or 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.

Minor editorial:

Patent information has been added to the end of the package circular.

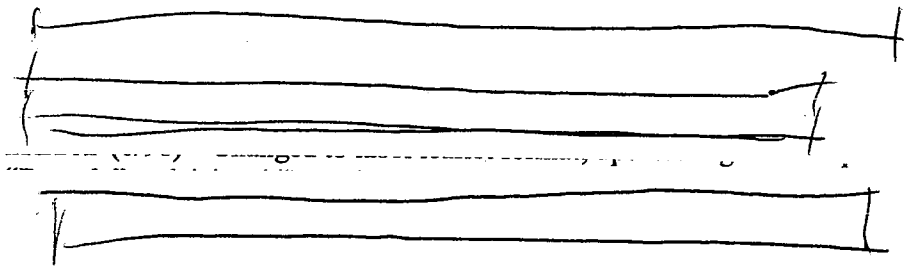
NDA 19-111
Tussionex® Extended-Release Suspension
Special Supplement – Changes Being Effected

This labeling revision (version LR242A) is being submitted as a "Special Supplement – Changes Being Effected" in accordance with the following:

> Pediatric Use Update: Per 21 CFR §314.70(c)(2)(i) to strengthen a warning or precaution
>
> Geriatric Use Update: Per FDA's Guidance for Industry, "Content and Format for Geriatric Labeling (October 2001)" and the Final Rule published in the *Federal Register* on August 27, 1997 (Vol. 62, No. 166, p. 45316) which state that the agency will not require prior approval of labeling changes for drug products under §201.57(f)(10)(ii)(A) where insufficient data exist to determine whether the responses of geriatric patients to a drug are different from the responses of younger patients.

To facilitate review, a copy of this labeling is also enclosed with the added text in Pediatric Use Geriatric Use subsections highlighted and compared to the current labeling for Tussionex.

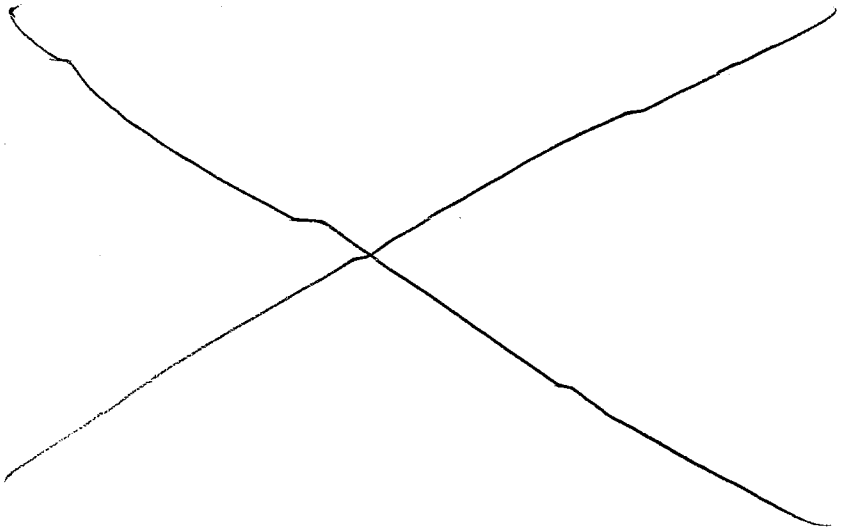
Please note that the most recent version of Tussionex labeling approved by the FDA was R240C (11/94) approved on Nov. 26, 1993 ("Changes Being Effected" supplement S-003, submitted on April 29, 1992). Subsequent updates included the following annual reportable changes:



Details of the data to support Geriatric Use labeling are provided in this section as follows:

Twelve (12) copies of final printed labeling (package circular LR242A) incorporating these revisions are enclosed in the archival copy of this submission. (Ten of these copies are individually mounted on heavy weight paper.)

Package Circular LR242A



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANTS NAME AND ADDRESS

Medeva Pharmaceuticals, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

2. TELEPHONE NUMBER *(Include Area Code)*

(585) 475-9000

3. PRODUCT NAME

Tussionex® Pennkinetic® Extended-Release Suspension

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS?** IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See *item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W
Washington, DC 20201

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Michele Bartlett	Michele Bartlett Director, Regulatory Affairs	09 May 03