CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-734

PHARMACOLOGY REVIEW

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-734
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	1/21/04
PRODUCT:	Children's ElixSure-24 hr Antihistamine
INTENDED CLINICAL POPULATION:	Children $\geq$ 2 years old.
SPONSOR:	Taro Pharmaceuticals, Inc.
DOCUMENTS REVIEWED:	None, since this NDA was submitted as a 505(b)(2).
REVIEW DIVISION:	Division of Pulmonary and Allergy Drug Products (HFD-570)
PHARM/TOX REVIEWER:	Lawrence F. Sancilio, Ph.D.
PHARM/TOX SUPERVISOR:	Ching-long J. Sun, Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Anthony Zeccola

Date of review submission to Division File System (DFS): 7/22/04

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Recommend approval.

B. Recommendation for nonclinical studies
None.

C. Recommendations on labeling
None, since this will be an over the counter product (OTC) which requires no preclinical section in the label.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
Loratadine is an approved prescription drug. There are no safety issues for potential adverse effects.

B. Pharmacologic activity
Loratadine is a potent H_1 receptor antagonist.

C. Nonclinical safety issues relevant to clinical use.
None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-734
Review number:1
Sequence number/date/type of submission: 000,1/19/04; 4/23/04
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Taro Pharmaceuticals U.S.A., Inc.
Five Skyline Drive
Hawthorne, NY 10532

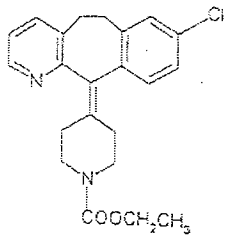
Manufacturer for drug substance:

[redacted]

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: Division of Pulmonary and Allergy Drug Products

HFD #: 570
Review completion date: 7/22/04

Drug:
Trade name: Children's ElixSure-24 hr Antihistamine
Generic name: Loratadine
Code name: Sch29851
Chemical name: Ethyl 4-(8-chloro-5, 6-dihydro-11H-benzo [5, 6] cyclohepta [1, 2-b] pyridin-11-ylidene)-1-piperidinecarboxylate
CAS registry number: 79794-75-5
Mole file number: Unknown
Molecular formula/molecular weight: $C_{22}H_{23}ClN_2O_2$/382.89
Structure:



Drug class: H_1 Receptor Antagonist

Relevant NDA: NDA 20-641

Drug class: H_1 Receptor Antagonist

Intended clinical population: Children 2 years of age and older [redacted]

Clinical formulation: Suspension. The composition is shown in the following table.

Appears This Way
On Original

Ingredient	mg/5ml
Loratadine	5
Purified water, USP	
Sodium Hydroxide	
Carbomer 934P (Carbopol ™ 974P), NF	
Sorbitol crystalline, NF	
Poloxamer 188, NF	
Propylene glycol, USP	
Butylparaben, NF	
Glycerin, USP	
Sucralose liquid concentrate	
Masking agent[a]	
Peach Flavor	
Total	

The levels of all the excipients are GRAS or have been used in marketed products, and the daily exposures are acceptable.

Route of administration: Oral.

Daily Dose: Children 2-6 years old: 1 teaspoonful (5 mg); > 6 year sold, 2 teaspoonfuls (10 mg)

Studies reviewed within this submission: None. This NDA is a 505 (b)(2) submitted as a literature application. The submission includes the 10/13/95 Summary of approval for NDA 20-641.

2.6.2 PHARMACOLOGY: NA.

2.6.2.1 Brief summary: NA.

2.6.2.2 Primary pharmacodynamics: NA.

Mechanism of action: NA.

Drug activity related to proposed indication: NA.

2.6.2.3 Secondary pharmacodynamics: NA.

2.6.2.4 Safety pharmacology: NA.

Neurological effects: NA.

Cardiovascular effects: NA.

Pulmonary effects: NA.

Renal effects: NA.

Gastrointestinal effects: NA.

Abuse liability: NA.

Other: NA.

2.6.2.5 Pharmacodynamic drug interactions: NA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: NA.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: NA.

2.6.4.1 Brief summary: NA.

2.6.4.2 Methods of Analysis: NA.

2.6.4.3 Absorption: NA.

2.6.4.4 Distribution: NA.

2.6.4.5 Metabolism: NA.

2.6.4.6 Excretion: NA.

2.6.4.7 Pharmacokinetic drug interactions: NA.

2.6.4.8 Other Pharmacokinetic Studies: NA.

2.6.4.9 Discussion and Conclusions: NA.

2.6.4.10 Tables and figures to include comparative TK summary: NA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY: NA.

2.6.6 TOXICOLOGY: NA.

2.6.6.1 Overall toxicology summary: NA.

General toxicology: NA.

Genetic toxicology: NA.

Carcinogenicity: NA.

Reproductive toxicology: NA.

Special toxicology: NA.

2.6.6.2 Single-dose toxicity: NA.

2.6.6.3 Repeat-dose toxicity: NA.

2.6.6.4 Genetic toxicology: NA.

2.6.6.5 Carcinogenicity: NA.

2.6.6.6 Reproductive and developmental toxicology: NA.

2.6.6.7 Local tolerance: NA.

2.6.6.8 Special toxicology studies: NA.

2.6.6.9 Discussion and Conclusions: NA.

2.6.6.10 Tables and Figures: NA.

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS: Loratadine is a potent orally active and selective H_1 receptor antagonist. From a preclinical standpoint, there are no safety or toxicity issues that would prevent loratadine from being an OTC product for children and adults. The levels of the excipients in the proposed suspension are acceptable.

Unresolved toxicology issues (if any): NA.

Recommendation: Approval of NDA 21-734.

Suggested labeling: NA.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Appendix/attachments: None.

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

/s/

Lawrence Sancilio
7/22/04 02:55:32 PM
PHARMACOLOGIST

Joseph Sun
7/22/04 03:44:43 PM
PHARMACOLOGIST
I concur.