

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-891

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Amendment

NDA number: 21-891

Date/type of submission: 8/2/05, 4/26/06

Date of Amendment: 7/24/06

In the Summary of nonclinical findings under Executive Summary, _____ should be replaced by loratadine as indicated below.

A. Brief Overview of Nonclinical Findings

References have been made to its toxicological profile in NDA 19-658 and NDA 20-641. In chronic oral toxicity studies up to 12 months in rats and up to 17 months in monkeys, the targeted organs were the testes, liver and lymphocytes. _____ **Loratadine** was not genotoxic, and in reproductive studies, _____ **loratadine** was not teratogenic but decreased male fertility and pup survival. In carcinogenicity studies, _____ - **loratadine** caused an increase in hepatocellular tumors in rats and mice. The clinical significance of these tumor findings during long term use is unknown.

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____

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/s/

Lawrence Sancilio
7/25/2006 11:27:15 AM
PHARMACOLOGIST

Joseph Sun
7/25/2006 03:21:17 PM
PHARMACOLOGIST
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-891

PHARMACOLOGY REVIEW(S)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-891
SERIAL NUMBERS: 000, 008
DATES RECEIVED BY CENTER: 8/2/05, 4/26/06
PRODUCT: Claritin Chewable tablet
INTENDED CLINICAL POPULATION: Children \geq 2 years old.
SPONSOR: Schering-Plough Health Care Products
DOCUMENTS REVIEWED: None.
REVIEW DIVISION: Division of Pulmonary and Allergy Products
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: E. Abraham

Date of review submission to Division File System (DFS): 5/23/06

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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 data in the label.

II. Summary of nonclinical findings

- A. Brief Overview of Nonclinical Findings
References have been made to its toxicological profile in NDA 19-658 and NDA 20-641. In chronic oral toxicity studies up to 12 months in rats and up to 17 months in monkeys, the targeted organs were the testes, liver and lymphocytes _____ as not genotoxic, and in reproductive studies, _____ was not teratogenic but decreased male fertility and pup survival. In carcinogenicity studies, _____ caused an increase in hepatocellular tumors in rats and mice. The clinical significance of these tumor findings during long term use is unknown.
- B. Pharmacologic activity
Loratadine is a potent H₁ receptor antagonist.
- A. Nonclinical safety issues relevant to clinical use.
There are no safety issues for potential adverse effects.

APPEARS THIS WAY
ON ORIGINAL

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-891

Review number: 1

Sequence number/date/type of submission: 8/2/05, Original

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Schering-Plough Health Care Products

Manufacturer for drug substance: Schering-Plough

Reviewer name: Lawrence F. Sancilio, Ph.D.

Division name: Division of Allergy and Pulmonary Products

HFD #: 570

Review completion date: 5/23/06

Drug:

Trade name: Claritin Chewable Tablets

Generic name: Loratadine

Code name: Sch29851

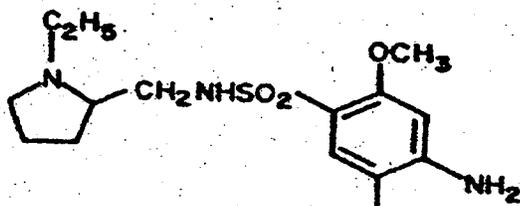
Chemical name: Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo [5,6] cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidinecarboxylate

CAS registry number: 79794-75-5

Mole file number: Unknown

Molecular formula/molecular weight: C₂₂H₂₃ClN₂O₂/382.89

Structure:



Relevant NDAs: NDA 19-658, NDA20-641

Drug class: H₁ Receptor Antagonist

Intended clinical population: _____

Clinical formulation: Chewable tablet.

The composition is shown in the following table.

Ingredient	mg/tablet
Loratadine	5
Mannitol, USP	
Aspartame	
: Flavor	
Citric Acid, Anhydrous, USP	
Dye, Blue #2 FD&C, Aluminum Lake	
Dye, Red #27 D&C, Aluminum Lake	
Collodion Silicon Dioxide, NF	
Sodium Starch,	
Stearic acid, NF/FG	
Magnesium Stearate, NF	

The levels of all the excipients are acceptable and safe.

Route of administration: Oral.

Daily Dose: Children from 2 to 6 years the dose is 5 mg every 24 hours; children over 6 years and adults, the dose is 10 mg every 24 hrs. This is the same daily dose as the Children's Claritin Syrup, and is being offered as an alternative to the Children's Claritin Syrup.

Studies reviewed within this submission: None. References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

References have been made to summaries in NDA 19-658 and NDA 20-641.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

Drug activity related to proposed indication: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.2.3 Secondary pharmacodynamics

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.2.4 Safety pharmacology

Neurological effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

Cardiovascular effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

Pulmonary effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

Renal effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

Gastrointestinal effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

Abuse liability: NA.

Other: NA.

2.6.2.5 Pharmacodynamic drug interactions

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

References have been made to summaries in NDA 19-658 and NDA 20-641.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.4.1 Brief summary

References have been made to summaries in NDA 19-658 and NDA 20-641.

2.6.4.2 Methods of Analysis: NA.

2.6.4.3 Absorption

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.4.4 Distribution

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.4.5 Metabolism

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.4.6 Excretion

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.4.7 Pharmacokinetic drug interactions

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.4.8 Other Pharmacokinetic Studies: NA.

2.6.4.9 Discussion and Conclusions

References have been made to NDA 19-658 and NDA 20-641.

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

2.6.5 PHARMACOKINETICS TABULATED SUMMARY: NA.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

References have been made to summaries in NDA 19-658 and NDA 20-641.

2.6.6.2 Single-dose toxicity

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.3 Repeat-dose toxicity

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.4 Genetic toxicology

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.5 Carcinogenicity

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.6 Reproductive and developmental toxicology

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.7 Local tolerance

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.8 Special toxicology studies

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-641.

2.6.6.9 Discussion and Conclusions

References have been made to NDA 19-658 and NDA 20-641.

2.6.6.10 Tables and Figures: NA.

2.6.7 TOXICOLOGY TABULATED SUMMARY: NA.

OVERALL CONCLUSIONS AND RECOMMENDATIONS: Loratadine is a potent orally active and selective H₁ receptor antagonist. From a preclinical standpoint, there are no safety issues that would prevent Claritin Chewable tablets 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): None.

Recommendation: Approval of NDA 21-891.

Suggested labeling: NA.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

Appendix/attachments: None.

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/s/

Lawrence Sancilio
5/23/2006 02:27:36 PM
PHARMACOLOGIST

Joseph Sun
5/23/2006 02:53:56 PM
PHARMACOLOGIST
I concur.