

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-993**

**PHARMACOLOGY REVIEW(S)**

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER: 21-993  
SERIAL NUMBER: 000, 002  
DATE RECEIVED BY CENTER: 2/10/06, 4/11/06  
PRODUCT: Claritin 5 mg RediTabs  
INTENDED CLINICAL POPULATION: Adults and children  $\geq$  6 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: N. Patel

Date of review submission to Division File System (DFS): 9/19/06

**APPEARS THIS WAY  
ON ORIGINAL**

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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. 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 which was reversible with cessation of dosing. 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.
- B. Pharmacologic activity  
Loratadine is a potent H<sub>1</sub> 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:** 21-993

**Review number:** 1

**Sequence number/date/type of submission:** 000, 002; 2/10/06, 4/11/06

**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

**Review completion date:** 9/18/06.

#### Drug:

**Trade name:** Claritin RediTabs

**Generic name:** Loratadine

**Code name:** Sch29851

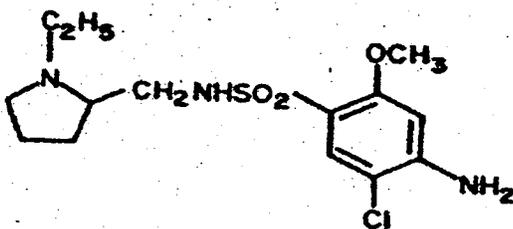
**Chemical name:** Ethyl 4-(8-chloro-5, 6-dihydro-1H-benzo [5, 6] cyclohepta [1, 2-b] pyridin-11-ylidene)-1-piperidinecarboxylate

**CAS registry number:** 79794-75-5

**Mole file number:** Unknown

**Molecular formula/molecular weight:** C<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>/382.89

**Structure:**



**Relevant NDAs:** NDA 19-658 and NDA 20-704.

**Drug class:** H<sub>1</sub> Receptor Antagonist

**Intended clinical population:** Treatment of the symptoms of allergic rhinitis in adults and in children 6 years and older.

**Clinical formulation:** RediTabs.

The composition is shown in the following table.

<b>Ingredient</b>	<b>mg/tablet</b>
Loratadine USP	5
Gelatin NF	—
Mannitol USP	—
Flavor Mint	—
Anhydrous Citric Acid USP	—

The levels of all the excipients are acceptable and safe. They are the same excipients used in NDA 20-704, the 10 mg oral disintegrating tablet.

**Route of administration:** Oral.

**Daily Dose:** Adults and children, 6 years and over, one tablet (5 mg) every 12 hours.

**Studies reviewed within this submission:** None. References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.2 PHARMACOLOGY****2.6.2.1 Brief summary**

References have been made to summaries in NDA 19-658 and NDA 20-704.

**2.6.2.2 Primary pharmacodynamics**

Mechanism of action: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

Drug activity related to proposed indication: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.2.3 Secondary pharmacodynamics**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.2.4 Safety pharmacology**

Neurological effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

Cardiovascular effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

Pulmonary effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

Renal effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

Gastrointestinal effects: References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

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 20-704.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY**

References have been made to summaries in NDA 19-658 and NDA 20-704.

**2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.4.1 Brief summary**

References have been made to summaries in NDA 19-658 and NDA 20-704.

**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 20-704.

**2.6.4.4 Distribution**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.4.5 Metabolism**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.4.6 Excretion**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.4.7 Pharmacokinetic drug interactions**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**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 20-704.

**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 20-704.

**2.6.6.2 Single-dose toxicity**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.3 Repeat-dose toxicity**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.4 Genetic toxicology**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.5 Carcinogenicity**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.6 Reproductive and developmental toxicology**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.7 Local tolerance**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.8 Special toxicology studies**

References have been made to preclinical reports and summaries in NDA 19-658 and NDA 20-704.

**2.6.6.9 Discussion and Conclusions**

References have been made to NDA 19-658 and NDA 20-704.

**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 H<sub>1</sub> receptor antagonist. From a preclinical standpoint, there are no safety issues that would prevent Claritin RediTabs 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 21-993.

Suggested labeling: NA.

Signatures (optional):

Reviewer Signature \_\_\_\_\_

Supervisor Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

Appendix/attachments: None.

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/s/

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Lawrence Sancilio  
9/19/2006 01:07:00 PM  
PHARMACOLOGIST

Joseph Sun  
9/19/2006 03:29:58 PM  
PHARMACOLOGIST  
I concur.