CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-605

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-605**
SERIAL NUMBER:	**N000**/April 30, 2004/Original NDA N000/October 1, 2004/BZ N000/December 2, 2004/BZ February 10, 2005 supplement – rationale for exposure ratios between mice and humans in the nonclinical sections of the labeling
DATE RECEIVED BY CENTER:	MAY 05, 2005
PRODUCT:	**Clarinex®-D 24 Hour Extended Release Tablets**
INTENDED CLINICAL POPULATION:	**Allergic Rhinitis**
SPONSOR:	**Schering Corporation**
DOCUMENTS REVIEWED:	**Original Filing**
REVIEW DIVISION:	**Pulmonary and Allergy Drug Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy McGovern, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Anthony Zeccola**

Date of review submission to Division File System (DFS): February 16, 2005

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Approval is recommended pending the proposed labeling revision.

B. Recommendation for nonclinical studies
None.

C. Recommendations on labeling
Revise the section of Carcinogenesis, Mutagenesis, Impairment of Fertility of the labeling submitted on December 2, 2004 as noted below. A detailed description of recommended deletions from and insertions to the sponsor's proposed labeling can be found on page 19.

PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility:

There are no animal or laboratory studies on the combination product of desloratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential of desloratadine was assessed using a loratadine study in rats and a desloratadine study in mice. In a 2-year study in rats, loratadine was administered in the diet at doses up to 25 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 30 times the AUC in humans at the recommended daily oral dose). A significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day and in males and females given 25 mg/kg/day. The estimated desloratadine and desloratadine metabolite exposures of rats given 10 mg/kg/day of loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.

In a 2-year dietary study in mice, males and females given up to 16 mg/kg/day and 32 mg/kg/day of desloratadine, respectively, did not show significant increases in the incidence of any tumors. The estimated desloratadine and metabolite exposures of mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

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II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

A recently-completed Phase-4 commitment carcinogenicity study shows that desloratadine is non-carcinogenic in mice. The study was submitted and reviewed under 21-165. The current application addresses the study because this is first time to describe the study results in the labeling of any desloratadine products.

CD-1 mice (50/sex/dose) were treated orally with dietary desloratadine for up to 101 weeks to evaluate the carcinogenic potential of the drug. The respective desloratadine doses were 4, 16 and 48 mg/kg/day in the males and 10, 32 and 96 mg/kg/day in the females. The low- and mid-dose mice were treated for 101 weeks prior to sacrifice. The high dose group was treated for up to 61 weeks; the treatment was terminated; and the surviving mice were observed until their sacrifice at week 101. Plasma desloratadine levels increased proportionally to the dose. No significant increase in the tumor incidence was observed in any of the treatment groups. Desloratadine is considered non-carcinogenic in mice under the testing condition.

B. Pharmacologic activity
Not applicable to this review. See original NDA review.

C. Nonclinical safety issues relevant to clinical use
None.

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2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

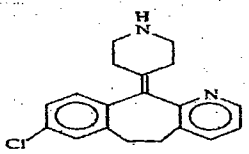
NDA Number: 21-605
Review Number : 1
Sequence number/date/submission type:
000/April 30, 2004/Original NDA
000/October 1, 2004 BZ
000/December 2, 2004/BZ
February 10, 2005 supplement

Information to the Sponsor: Yes (X), No ( )
Sponsor/or Agent: Schering Corporation
Manufacturer of the Drug Substance: Schering Corporation

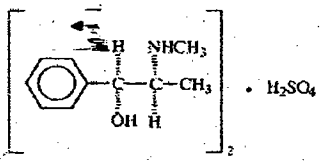
Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Drug Products
HFD #: HFD-570
Review Completion Date: February 16, 2005

Drug:
Trade Name: Clarinex®-D 24 Hour Extended Release Tablets
Generic Name: Desloratadine 5 mg and Pseudoephedrine 240 mg
Code Name: SCH 483 (combination product); SCH 34117 or DCL for desloratadine and PSE for pseudoephedrine
Chemical Name: DCL: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinyllidene),
PSE: α-[1-(methylamino) ethyl]-[S-(R*,R*)]-benzenemethanol sulfate (2:1) (salt)
CAS Register Number: N/A
Molecular Form and Weight: DCL: $C_{19}H_{19}ClN_2$
PSE: $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$
Structure:

Desloratadine:



Pseudoephedrine:



Relevant IND/NDAs/DMFs: INDs 55,364, 21,249, 41,897 and 58,506
NDAs 19-658 (loratadine), 21-165, 21-297, 21-300, 21-312, 21-313, 21-363 & 21-563

Drug Class: Antihistamine

Intended clinical population: Allergic rhinitis in children 12 years of age and adults (5 mg DCL once daily)

Clinical Formulation: (Per tablet) 5 mg desloratadine, 240 mg pseudophedrine, [redacted] hypromellose methylcellulose, [redacted], [redacted] povidone [redacted], [redacted] silicone dioxide, [redacted] magnesium stearate

Route of Administration: Oral (tablets)

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Studies Submitted and Reviewed in the Review: None.

Studies Submitted but Not Reviewed in this Review: None.

Background:

Desloratadine (Clarinex®) is a currently marketed H_1-histamine receptor antagonist indicated for allergic rhinitis and urticaria in adults and children of 6 months of age or older. The first desloratadine product was approved in December 21, 2001. The recommended dose of desloratadine is 5 mg per day in adults and children 12 years of age or older. Pediatric use of the drug was approved recently on September 1, 2004. Dosage in younger children is adjusted for body weight. The plasma desloratadine AUCs in adults and of in these patients are similar to that in adults.

Table 1. Desloratadine Products on the Market or in Development

NDA No.	Clarinex® Dosage	Indication	Status	Approval Date
21-165	Tablets	Allergic rhinitis	AP	21-DEC-01
21-297	Tablets	Idiopathic urticaria	AP	08-FEB-02
21-300	Syrup (2 – 11 yr)	Allergic rhinitis & urticaria	AP	01-SEP-2004
21-312	Reditab®	Allergic rhinitis & urticaria	AP	26-JUN-04
21-313	Tablets – D [a]	Allergic rhinitis & congestion	AE	
21-363	Tablets	Allergic rhinitis	AP	08-FEB-02
21-563	Syrup (0.5 – 11 yr)	Allergic rhinitis & urticaria	AP	01-SEP-2004
21-605	D-24 tablets	Allergic rhinitis & congestion	PN	Under review

a. Each tablet also contains 120 mg pseudoephedrine.

An application (Clarinex D, NDA 21-313) for the combination of desloratadine (5 mg) and pseudoephedrine (120 mg) is pending. Dr. Timothy McGovern conducted a pharmacology

and toxicology review of Clarinex D on October 23, 2001. The current application differs from NDA 21-313 regarding the pseudoephedrine dose (240 mg/Clarinex D-24 tablet vs. 120 mg/Clarinex D tablet). Similar to NDA 21-313, this nonclinical safety review of the current application concentrates on the safety of desloratadine. The reason is that the safety of pseudoephedrine has been established nonclinically and clinically and there are no expected adverse interactions between desloratadine and pseudoephedrine.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

No additional information was submitted. Dr. Timothy McGovern reviewed the pharmacology of desloratadine on September 29, 2000 in NDA 12-165. Desloratadine is a selective H_1-receptor antagonist that is currently marketed in the US (approval date of 21-DEC-2001). Desloratadine inhibits the release of IL-4 and IL-13, and IL-6 and IL-8, histamine, tryptase, LTC_4 and PGD_2, and RANTES and attenuates eosinophil chemotaxis and adhesion. It also inhibits superoxide anion production by PMN, histamine-induced activation of endothelial cells, and P-selectin expression.

Pseudoephedrine is an alpha adrenergic receptor agonist that is currently marketed as a nasal decongestant in many drug products. Co-administration of pseudoephedrine prolongs the action of duration of desloratadine.

2.6.2.2 Primary pharmacodynamics

No additional information was submitted. All pharmacology studies were reviewed under NDA 21-165. Desloratadine is a selective H_1-receptor antagonist that is currently marketed in the US (approval date of 21-DEC-2001). Desloratadine inhibits the release of IL-4 and IL-13, and IL-6 and IL-8, histamine, tryptase, LTC_4 and PGD_2, and RANTES and attenuates eosinophil chemotaxis and adhesion.

2.6.2.3 Secondary pharmacodynamics

No additional information was submitted. All pharmacology studies were reviewed under NDA 21-165. Desloratadine inhibits superoxide anion production by PMN, histamine-induced activation of endothelial cells, and P-selectin expression. Desloratadine also expresses a high affinity for cloned human M_1 and M_3 receptor subtypes (IC_{50} = 48 and 125 nM).

2.6.2.4 Safety pharmacology

No additional information was submitted. All pharmacology studies were reviewed under NDA 21-165. Appropriate safety pharmacology studies were performed with desloratadine

and no significant concerns were observed. Desloratadine has less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K+ channels as well as a cloned human hKv1.5. In addition, all positive cardiac findings were observed during *in vitro* assessments while *in vivo* studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters.

2.6.2.5 Pharmacodynamic drug interactions

No information was submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no information was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

No additional information was submitted. Dr. Timothy McGovern reviewed the pharmacokinetics and toxicokinetics of desloratadine on September 29, 2000 in NDA 21-165. Desloratadine is generally well absorbed after oral administration. Its oral bioavailability is 45-94% in rats and 47-57% in monkeys. Plasma concentrations of desloratadine increase supra-proportionally with dose in rats and monkeys. Tmax is achieved within 4 hours in rabbits, mice and monkeys and 1.5-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. In rats, desloratadine is widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Plasma protein binding of desloratadine is variable across species as the mouse, rat, monkey and humans demonstrates 94.4%, 90.5%, 85.8% and 85.0% binding, respectively.

Desloratadine is extensively metabolized in rats, mice and monkeys. The metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products. Metabolism of desloratadine occurs through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position is more extensive in humans. Male rats achieve relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. Excretion of desloratadine-related radioactivity is primarily through the feces with a large portion contributed through the bile. Approximately 20-40% is excreted through the urine.

2.6.4.2 Methods of Analysis

No information submitted.

2.6.4.3 Absorption

Dr. Timothy McGovern reviewed the pharmacokinetics and toxicokinetics of desloratadine on September 29, 2000 in NDA 21-165. Desloratadine is generally well absorbed after oral administration. Its oral bioavailability is 45-94% in rats and 47-57% in monkeys. Plasma concentrations of desloratadine increase supra-proportionally with dose in rats and monkeys. Tmax is achieved within 4 hours in rabbits, mice and monkeys and 1-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. In rats, desloratadine is widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Plasma protein binding of desloratadine is variable across species as the mouse, rat, monkey and humans demonstrates 94.4%, 90.5%, 85.8% and 85.0% binding, respectively.

2.6.4.4 Distribution

Dr. Timothy McGovern reviewed the pharmacokinetics and toxicokinetics of desloratadine on September 29, 2000 in NDA 21-165. In rats, desloratadine was widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Distribution of ^{14}C-loratadine in pregnant rats demonstrated that radioactivity crossed the placental barrier equally at the post-embryonic period and near-term. Tissue distribution was similar in maternal and fetal tissues with lower levels found in the fetus.

2.6.4.5 Metabolism

Dr. Timothy McGovern reviewed the pharmacokinetics and toxicokinetics of desloratadine on September 29, 2000 in NDA 21-165. Desloratadine is extensively metabolized in rats, mice and monkeys. The metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products. Metabolism of desloratadine occurs through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position is more extensive in humans. Male rats achieve relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys.

2.6.4.6 Excretion

Dr. Timothy McGovern reviewed the pharmacokinetics and toxicokinetics of desloratadine on September 29, 2000 in NDA 21-165. Excretion of desloratadine-related radioactivity was primarily through the feces with a large portion contributed through the bile. Approximately 20-40% was excreted through the urine.

2.6.4.7 Pharmacokinetic drug interactions

No information was submitted.

2.6.4.8 Other Pharmacokinetic Studies

No information submitted.

2.6.4.9 Discussion and Conclusions

Nonclinical characterization of pharmacokinetics and toxicokinetics of desloratadine in animals has been completed NDA 21-165. No additional nonclinical formation was submitted.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

No additional information is submitted. The following summary is based on the previous reviews. These reviews are: 1) the original NDA review of desloratadine by Dr. Timothy McGovern on September 29, 2000 in NDA 21-165, 2) a review of the carcinogenic potential of desloratadine in mice by Dr. Luqi Pei on January 25, 2005 in NDA 21-165, and 3) the original NDA review of Clarinex D tablets (desloratadine and pseudoephedrine combination) by Dr. T. McGovern on October 23, 2001 in NDA 21-313.

General toxicology: Desloratadine causes phospholipidosis in multiple organs in the laboratory animals. Toxicity of desloratadine has been evaluated in mice, rats and monkeys for up to 3-months duration. These studies demonstrate that the toxicological profiles of desloratadine and loratadine are similar. The primary toxicity finding of desloratadine is systemic phospholipidosis in organ and systems throughout the body. In mice, phospholipidosis occurs at 96 mg/kg/day and mortality occurs at 192 mg/kg/day after two

months of treatment. In rats, treatment-related mortality occurs at a dose of 120 mg/kg in males and 30 mg/kg or greater in females in a three month study. Systemic phospholipidosis is the primary toxicity finding in tissues throughout the body. In addition, kidney necrosis and luminal cellular debris of the epididymides are also observed. The NOAEL in the 3-month toxicity study is 3 mg/kg in females and 30 mg/kg in males. These doses correlate to mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 1890 ng.hr/ml and 9490 ng.hr/ml in females and males, respectively. In monkeys, no treatment-related mortality occurs at doses up to 18 mg/kg for 3 months. Phospholipidosis is again the primary toxicity finding in organs/tissues throughout the body. The NOAEL in the 3-month toxicity study is 12 mg/kg which results in mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 21,613 ng.hr/ml.

Carcinogenicity: The carcinogenicity of desloratadine is evaluated in traditional bioassays in mice and rats. Desloratadine is non-carcinogenic in mice and equivocal in rats. There were two carcinogenicity studies in mice. The first study was an 18-month loratadine study. Desloratadine is a metabolite of loratadine in vivo. Mice treated with loratadine are exposed to desloratadine to some degree. Male mice given 40 mg/kg/day of loratadine showed a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas). The results are described in the labeling of the desloratadine products currently on the market.

The second study (Study SN 97255) is a 2-year dietary carcinogenicity study conducted as a phase 4 commitment for the approval of NDA 21-165. Desloratadine at oral doses up to 16 mg/kg/day in males and 32 mg/kg/day in females for 101 weeks did not cause significant increases in the incidence of any tumors. Neither was there a significant increase in any tumor incidence at 48 mg/kg/day for 56 weeks in the males and 96 mg/kg/day for 61 weeks in the females. The study did not reveal any evidence of carcinogenic potential of desloratadine in mice under the conditions tested. Presentation of the carcinogenic potential of desloratadine in mice in the labeling is discussed later in the section of labeling review.

In rats, males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas). The plasma levels of desloratadine in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans receiving 5 mg desloratadine as Clarinex. The results are described in the labeling of the desloratadine products currently on the market.

2.6.6.2 Single-dose toxicity

Not applicable. See NDA review by Dr. Timothy McGovern dated September 29, 2000 in NDA 21-165.

2.6.6.3 Repeat-dose toxicity

Not applicable. See NDA review by Dr. Timothy McGovern dated September 29, 2000 in NDA 21-165.

2.6.6.4 Genetic toxicity

Not applicable beeause no information was submitted. Dr. Timothy McGovern reviewed the genetic toxicology of desloratadine in the review on September 29, 2000 in NDA 21-165. Desloratadine tests negative in the following assays: the bacterial mutation in *S. typhimurium and E. coli* (Ames test), *in vitro* chromosome aberration assay using human lymphocytes, and *in vivo* mouse bone marrow erythrocyte micronucleus assay.

2.6.6.5 Carcinogenicity

The carcinogenicity of desloratadine is evaluated in 2-year traditional bioassays in mice and rats. Desloratadine is non-carcinogenic in mice and equivocal in rats. There were two carcinogenicity studies in mice. The evaluation of the carcinogenic potential of desloratadine in the mice can be found in the labeling review section.

The first study was a 18-month loratadine in which the mice had a certain degree of exposure to desloratadine. Male mice given 40 mg/kg/day of loratadine showed a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas). The plasma levels of desloratadine and its metabolites in mice receiving 40 mg/kg/day of loratadine were approximately 3 times that in humans. The results are described in the labeling of the desloratadine products currently on the market.

The second study (SN 97-255) is a 2-year dietary carcinogenicity study in mice conducted as a phase-4 commitment for the approval of NDA 21-165. Desloratadine at oral doses up to 16 mg/kg/day in males and 32 mg/kg/day in females for 101 weeks did not cause significant increases in the incidence of any tumors. Neither was there significant increase in any tumor incidence at 48 mg/kg/day for 56 weeks in the males and 96 mg/kg/day for 61 weeks in the females.

In rats, males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas). The plasma levels of desloratadine in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans administered 5 mg desloratadine in with Clarinex. The results of the study are described in the labeling of currently marketed desloratadine products.

2.6.6.6 Reproductive and Developmental Toxicology:

No additional information is submitted. Dr. Timothy McGovern reviewed the effect of desloratadine on fetal-embryo development, peri- and post-natal development and fertility in a review dated September 29, 2000 in NDA 21-165. The findings have been described in the labeling of the approved desloratadine products. Dr. McGovern also addressed the reproductive and developmental effect of the desloratadine and pseudoephedrine combination in a review for NDA 21-313 dated October 23, 2001. The review concludes no additional data is needed once desloratadine is approved for marketing. The Agency approved Desloratadine on December 21, 2001. The reproductive and developmental toxicology of desloratadine and pseudoephedrine combination is considered adequately addressed.

2.6.6.7 Local tolerance

No information was submitted.

2.6.6.8 Special toxicology studies

No information was submitted.

2.6.6.9 Discussion and Conclusions

There are no animal or laboratory studies on the combination product of desloratadine and pseudoephedrine sulfate to evaluate the general toxicity, carcinogenesis, mutagenesis, impairment of fertility, and reproductive toxicity. Available information about desloratadine was obtained in the desloratadine NDA (NDA 21-165).

Oral administration of desloratadine causes phospholipidosis in multiple organs in the laboratory animals. Toxicity of desloratadine has been evaluated in mice, rats and monkeys for up to 3-months duration. These studies demonstrate that the toxicological profiles of desloratadine and loratadine are similar. The primary toxicity finding of desloratadine is systemic phospholipidosis in organ and systems throughout the body. In mice, phospholipidosis occurs at 96 mg/kg/day and mortality occurs at 192 mg/kg/day after two months of treatment. In rats, treatment-related mortality occurs at a dose of 120 mg/kg in males and 30 mg/kg or greater in females in a three month study. Systemic phospholipidosis is the primary toxicity finding in tissues throughout the body. In addition, kidney necrosis and luminal cellular debris of the epididymides are also observed. The NOAEL in the 3-month toxicity study is 3 mg/kg in females and 30 mg/kg in males. These doses correlate to mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 1890 ng.hr/ml and 9490 ng.hr/ml in females and males, respectively. In monkeys, no treatment-related mortality occurs at doses up to 18 mg/kg for 3 months. Phospholipidosis is again the primary toxicity finding in organs/tissues throughout the body. The NOAEL in the 3-month toxicity study is 12 mg/kg which results in mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 21,613 ng.hr/ml.

The carcinogenicity of desloratadine is evaluated in traditional bioassays in mice and rats. Desloratadine is non-carcinogenic in mice and equivocal in rats. The effects of desloratadine on fetal-embryo development, peri- and post-natal development and fertility have been described in the labeling of the approved desloratadine products.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The approval for the Clarinex D-24 application is recommended from the nonclinical discipline, pending recommended labeling revision. The sponsor has established the nonclinical safety of the Clarinex D-24, a combination product of desloratadine and pseudoephedrine. Desloratadine and pseudoephedrine individually are approved drugs on the market. Desloratadine is indicated for allergic rhinitis while pseudoephedrine is a nasal decongestant. Extensive clinical experience of the individual drugs is available. Combination use of pseudoephedrine and non-desloratadine antihistamines for rhinitis, including loratadine (Claritin), is well known. There are no expected drug interactions between desloratadine and pseudoephedrine. There are no outstanding nonclinical issues. An approval is recommended, pending the recommended labeling revision.

Safety evaluations of desloratadine and pseudoephedrine combination are available. Dr. Timothy McGovern conducted the nonclinical safety of desloratadine in a review dated September 29, 2000 in NDA 21-165. Extensive clinical experience has established the safety of pseudoephedrine. Dr. Timothy McGovern also conducted the nonclinical safety evaluation of desloratadine (5 mg) and pseudoephedrine (120 mg) combination in a review dated October 23, 2001 in NDA 21-313 (Clarinex D, Attachment A). The review concluded that no additional nonclinical data is needed for such a combination if desloratadine is an approved product on the market. Although the pseudoephedrine dose (240 mg) in the current product, Clarinex D-24, is twice that of Clarinex D (120 mg), the proposed dose of pseudoephedrine is similar to other approved drug products (i.e., Claritin D 24 and Allergra-D, 120 mg/tablets, two tablets per day). The available data have established the nonclinical safety of Clarinex D24.

In a filability review of the application dated June 24, 2004, Dr. Luqi Pei recommended updating the labeling for desloratadine to include a recently completed 2-year carcinogenicity study of the drug in mice (Study SN 97255). The sponsor submitted updated labeling in submissions dated October 1 and December 2, 2004. The current review has updated the labeling (below). There are no other outstanding issues, with the exception of the labeling review.

Unresolved toxicology issues: None

Recommendations:

This application is recommended for approval from a nonclinical perspective pending acceptance of recommended changes to the labeling regarding the description of carcinogenicity study results.

LABELING REVIEW:

This labeling review of Clarinex D-24 is based on available previous reviews of desloratadine labeling. The review does not address pseudoephedrine due to the lack of animal toxicity data of the compound and the extensive available clinical experience. Also, there are no nonclinical studies to evaluate the nonclinical safety of the desloratadine and pseudoephedrine combination. Furthermore, the review discusses the carcinogenesis section of the sponsor's proposed desloratadine labeling only. The other nonclinical sections of proposed labeling are identical to what has been approved and are acceptable; additional discussions are unnecessary. An exception is the addition of a qualification statement in the beginning of the relevant section that states there are no studies conducted with the combination of desloratadine and pseudoephedrine. The exception is also considered acceptable.

The Division has conducted the labeling review of desloratadine previously. These reviews of include reviews by Dr. Timothy McGovern on September 29, 2000 and Dr. Luqi Pei on January 25, 2005 for NDA 21-165, and by Dr. Pei on August 16, 2004 for NDAs 21-300 and 21-563. Dr. McGovern conducted the original labeling review of desloratadine. Dr. Pei recommended a labeling update to include a recently completed carcinogenicity study of desloratadine in mice (Study SN 97255) in NDA 21-165 (Attachment B). Dr. Pei's review in NDAs 21-300 and 21-563 addressed the difference in desloratadine metabolism among patient populations. The current review addresses the labeling update only.

The following sections present sequentially the text of the currently approved labeling, the sponsor's newly proposed text, the review of the new proposal, and the text proposed by the for the carcinogenesis section of desloratadine.

A. The currently approved labeling for the carcinogenesis of desloratadine

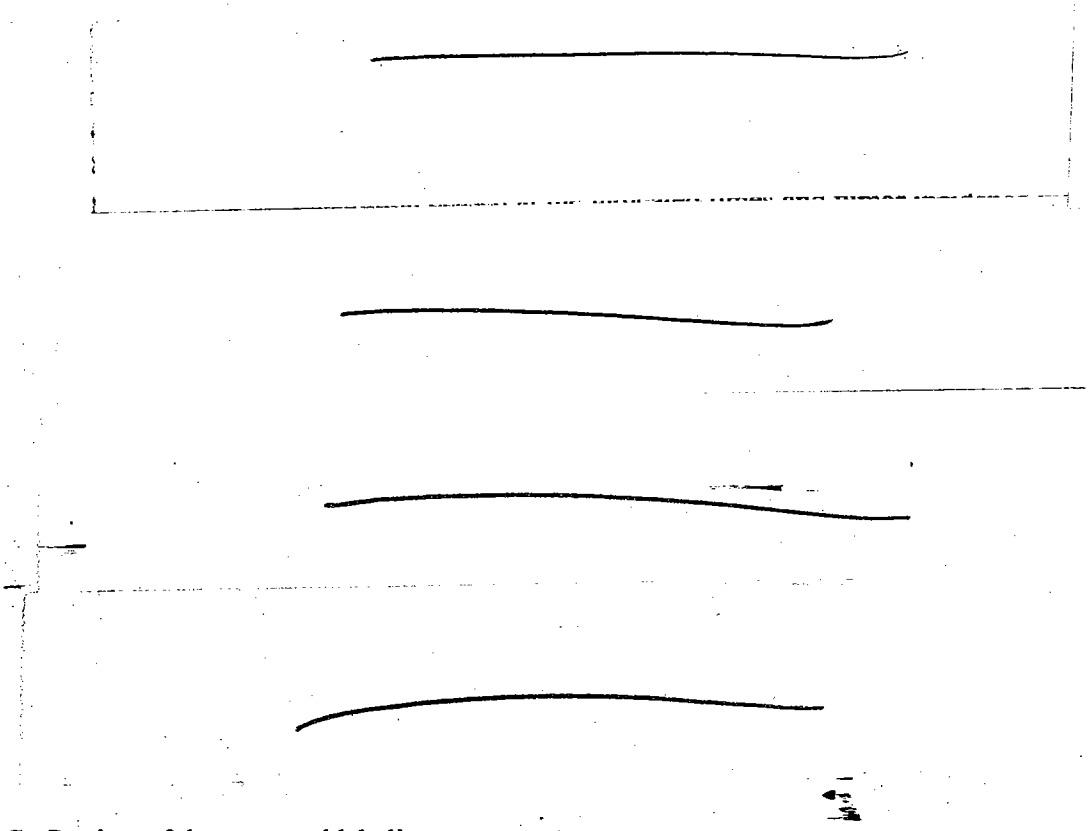
The carcinogenic potential of desloratadine was assessed using loratadine studies. In an 18-month study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg/day in mice (estimated desloratadine and desloratadine metabolite exposures were approximately 3 times the AUC in humans at the recommended daily oral dose) and 25 mg/kg/day in rats (estimated desloratadine and desloratadine metabolite exposures were approximately 30 times the AUC in humans at the recommended daily oral dose). Male mice given 40 mg/kg/day loratadine had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day and in males and females given 25 mg/kg/day. The estimated desloratadine and desloratadine metabolite exposures of rats given 10

mg/kg of loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.

B. Sponsor's newly proposed text for the carcinogenesis section of the labeling

The sponsor submitted the following text on October 1, 2004 and December 2, 2004.

> "There are no animal or laboratory studies on the combination product of desloratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.



C. Review of the proposed labeling

The following review evaluates the desloratadine dose ratios between mice and humans and the rationale to revise the findings in mice. The review is based on the submissions of October 1 and December 2, 2004, and February 10, 2005. The first two submissions are the proposed text for the labeling and the last the rationale for the estimates of desloratadine exposure ratios between mice and humans.

4 Page(s) Withheld

_____ Trade Secret / Confidential

8 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-_____

APPENDIX/ATTACHMENTS

ATTACHEMNT A.

Original Pharmacology and Toxicology NDA Review of Clarinex D (a Desloratadine and Pseudoephedrine Product)

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PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-313
Review number: 1
Sequence number/date/type of submission: NA/December 11, 2000/Original NDA
000/April 30, 2001/B2
Information to sponsor: Yes (✔) No ( )
Sponsor and/or agent: Schering Plough Corp., Kenilworth, NJ, USA
Manufacturer for drug substance: Schering Plough Corp., Kenilworth, NJ, USA

Reviewer name: Timothy J. McGovern, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: October 23, 2001

Drug:

Trade Name: CLARINEX-D 12 Hour Extended Release Tablet

Generic: Descarboethoxyloratadine (DCL, SCH 34117)/pseudoephedrine sulfate (PSE)

Code Name: SCH 483

Chemical name:

DCL: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinyllidene)

PSE: □-[1-(methylamino) ethyl]-[S-(R*,R*)]-benzenemethanol sulfate (2:1) (salt)

CAS registry number: NA

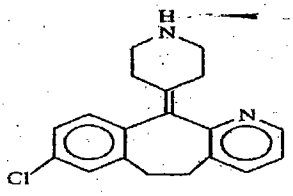
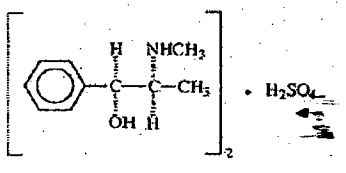
Mole file number: NA

Molecular formula/molecular weight:

DCL: $C_{19}H_{19}ClN_2$

PSE: $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$

Structure:

Desloratadine:	
Pseudoephedrine:	

Relevant INDs/NDAs/DMFs:
IND 55,364 Descarboethoxyloratadine tablets
IND 58,506 SCH 483-BID tablet
NDA 21-165 Clarinex (Seasonal allergic rhinitis)
NDA 21-297 Clarinex (chronic idiopathic urticaria)
NDA 21-300 Clarinex Syrup (Seasonal allergic rhinitis and chronic idiopathic urticaria)
NDA 21-312 Clarinex RediTab (Seasonal allergic rhinitis and chronic idiopathic urticaria)

Drug class: Anti-histamine

Indication: Seasonal allergic rhinitis and congestion

Clinical formulation: Tablet with immediate release formulation of DCL and extended release formulation of PSE:

Ingredient: DCL layer	mg/tablet	Ingredient: PSE layer	mg/tablet
DCL		PSE	
Corn starch NF			
		Microcrystalline cellulose NF	
Microcrystalline cellulose NF		Povidone USP	
		Silicon dioxide, NF	
Dye FD&C blue No. 2 aluminum lake		Magnesium stearate NF	
Nominal layer weight			
		Nominal layer weight	
Nominal Tablet weight			

*: Evaporates during manufacturing

Route of administration: Oral (tablet)

Proposed use: Adults and 12 years of age and over: The recommended dose of Clarinex-D 12 hour extended release tablets is one tablet twice a day. This is equal to a total of 5 mg desloratadine per day and 240 mg PSE per day. In a 50-kg adult this is equivalent to 0.1 mg/kg or 3.7 mg/m^2 desloratadine and 4.8 mg/kg or 177.6 mg/m^2 PSE.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Studies reviewed within this submission:
Study 00074: Three-month oral (gavage) toxicity study of SCH 34117 with degradants in rats. Submission 000 B2, Volume 4.3.
Study 00208: Three-month oral (gavage) toxicity study of SCH 34117 with degradants in cynomolgus monkeys. Submission 000 B2, Volume 4.6.
Study 00134: *Salmonella-Escherichia* / Mammalian-microsome reverse mutation assay with a confirmatory assay of SCH 34117 with degradants

[redacted]. Submission 000 B2, Volume 4.6.

Study 00135: Mouse bone marrow erythrocyte micronucleus study of SCH 34117 with degradants [redacted]. Submission 000 B2, Volume 4.6.

Studies not reviewed within this submission: None

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-313 is approvable from a preclinical perspective pending the approval of desloratadine in an alternate formulation or the submission of a 3-month bridging study and a teratology study with the combination of desloratadine and PSE.

B. Recommendation for Nonclinical Studies

Approval of this NDA requires a 3-month bridging general toxicity study in one species and a teratology study in one species with the desloratadine/PSE combination unless desloratadine is approved for marketing. In addition, a 2-year carcinogenicity study in mice should be completed as a Phase 4 commitment to further evaluate the carcinogenic potential of SCH 34117. The sponsor should submit the final study report within three years of the approval of NDA 21-165 or study initiation, whichever occurs first.

C. Recommendations on Labeling

The sponsor will be requested to submit updated labeling to conform, where applicable, to the final labeling for NDA 21-165. Thus, a review of the product label will be performed at a later time.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

General toxicology studies of up to 3 months duration were performed in rats and monkeys. The primary adverse finding was phospholipidosis, which was observed in tissues/organs throughout the body. The similar toxicological findings following SCH 34117 and loratadine administration in the 3-month rat and monkey studies at similar exposure levels of SCH 34117, the primary active metabolite of loratadine, support bridging to the chronic loratadine toxicology program. Therefore, the Sponsor was not required to perform chronic toxicity studies with SCH 34117. SCH 34117 tested negatively in the standard genetic toxicology battery. Carcinogenicity studies were not performed with SCH 34117. However, a 2-year study in rats performed with loratadine was deemed adequate to assess the carcinogenic potential of SCH 34117. The sponsor committed to perform a 2-year study in mice as a Phase 4 commitment. SCH 34117 induced a male-specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes at an oral dose of 12 mg/kg. An increase in pre-implantation and a decreased number of implantations and fetuses were noted in female rats; reduced body weight and slow righting reflex were noted in pups. SCH 34117 was not teratogenic at oral doses up to 48 mg/kg.

No nonclinical studies have been performed for pseudoephedrine sulfate. There is, however, extensive clinical experience with this compound and it is approved for use

in the indicated population in combination with loratadine, the parent compound of desloratadine.

B. Pharmacologic Activity

SCH 34117 demonstrated a high selectivity for H_1-receptors over H_2 or H_3-receptors. This finding was confirmed in isolated guinea pig lung tissue. SCH 34117 also demonstrated H_1-receptor activity in rat brain and was comparable in potency to its primary unconjugated metabolites. In an *in vitro* assessment of antihistaminic activity using guinea pig isolated ileum, SCH 34117 was up to 20-fold more potent than loratadine and was 4 to 8.5-fold more potent in inhibiting histamine-induced bronchospasm *in vivo*.

C. Nonclinical Safety Issues Relevant to Clinical Use

The safety of the combination of desloratadine and PSE has not been assessed in general toxicology or teratology studies. The sponsor was previously informed that a 3-month general toxicology study in one species and a teratology study in one species using the desloratradine/PSE combination would be needed for bridging purposes if desloratdine is not a marketed product. The original NDA for desloratadine (NDA 21-165) is currently considered to be Approvable.

III. Administrative

A. Reviewer signature: _____
Timothy J. McGovern, Ph.D.

B. Supervisor signature: Concurrence - _____
C. Joseph Sun, Ph.D.

C. cc: list:
D. Hilfiker
C.J. Sun
T.J. McGovern

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TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

All pharmacology studies were reviewed under IND 55,364 and NDA 21-165. See the attached reviews for the detailed study evaluations.

Pharmacology summary: SCH 34117 demonstrated a high selectivity for H_1-receptors over H_2 or H_3-receptors and displayed a 14-fold greater affinity for the H_1-receptor than loratadine in cloned H_1 human receptor subtypes (IC_{50} = 51 and 721 nM, respectively). This finding was confirmed in isolated guinea pig lung tissue (IC_{50} = 840 and 3030 nM for SCH 34117 and loratadine, respectively). SCH 34117 was also ~ 18-fold more potent than loratadine in rat brain H_1-receptor activity (SCH 34117 K_i = 4.8-7 nM) and was comparable in potency to its primary unconjugated metabolites. In an *in vitro* assessment of antihistaminic activity using guinea pig isolated ileum, SCH 34117 was up to 20-fold more potent than loratadine and was 4 to 8.5-fold more potent in inhibiting histamine-induced bronchospasm *in vivo* (SCH 34117 ED_{50} = 0.11-0.27 mg/kg, IV). *In vivo* studies performed for the loratadine program demonstrated that SCH 34117 was 2.5-4 times more potent than loratadine following oral administration in mice and guinea pigs. SCH 34117 also expressed a high affinity for cloned human M_1 and M_3 receptor subtypes (IC_{50} = 48 and 125 nM). In a separate study, SCH 34117 showed greatest activity at central H_1 receptors (IC_{50} = 17 nM) while activity at peripheral H_1 receptors was similar to that at M_2 muscarinic receptors (IC_{50} = 131-168 nM). Other receptor sites tested showed significantly reduced activity.

Pharmacology conclusions: Anti-histaminic activity has been demonstrated for SCH 34117. The results in the Clinical Pharmacology of the submitted labeling concerning the increased relative potency of SCH 34117 compared to loratadine are acceptable.

II. SAFETY PHARMACOLOGY:

All safety pharmacology studies were reviewed under IND 55,364 and NDA 21-165. See the attached reviews for the detailed study evaluations.

Safety pharmacology summary: SCH 34117 induced no effect on the rat central nervous system at oral doses up to 12 mg/kg. In vivo assessments of SCH 34117-related effects on cardiovascular function demonstrated that no significant in vivo cardiovascular effects were observed in rats or monkeys (doses up to 12 mg/kg, oral, or 10 mg/kg, intraperitoneal) or in guinea pigs (25 mg/kg SCH 34117, IV). In a study cited by the sponsor[1], loratadine (30 and 100 mg/kg, IV) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 µg/ml), in contrast to terfenadine, quinidine and diphenhydramine which induced significant cardiovascular and ECG effects. Resulting SCH 34117 concentrations (1.46 µg/ml) were 370-

[1] Hey, JA, Del Prado, M, Cuss, FM, Egan, RW, Sherwood, J, Lin, CC, and Kreutner, W. (1995). Antihistamine activity, central nervous system and cardiovascular profiles of histamine H1 antagonists: comparative studies with loratadine, terfenadine and sedating antihistamines in guinea-pigs. Clinical and Experimental Allergy, 25: 974-984.

fold greater than its C_{max} in man after a single oral dose of 10 mg loratadine. In vitro studies showed that SCH 34117 and loratadine were significantly less potent than terfenadine in inhibiting rat ventricular myocyte and guinea pig cardiac K^+ channels. SCH 34117 did exert effects on various cardiac parameters in vitro at concentrations ranging from 5-100 μM. SCH 34117 blocked hKv1.5 channels cloned from human ventricle and expressed in a mouse cell line (Ltk-), in a concentration-, voltage-, and time-dependent manner. SCH 34117 (1 to 100 μM) also inhibited a cloned human hKv1.5 current with an K_D of 12.5 μM, but was less potent than loratadine or terfenadine (K_D=1.0 and 0.8 μM, respectively). Thus, the relative potency is terfenadine > loratadine > SCH 34117. SCH 34117 was ~ 7-fold less potent than loratadine in blocking KV1.5 channel in HEK 293 cells and loratadine (10 □M) failed to significantly alter HERG currents. Both drugs (up to 10 □M) had minimal effects on I_{HERG} current (15-20%) compared to terfenadine and quinidine (IC50 = 82 and 168 nM, respectively). SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10 μM) in isolated rabbit hearts, due primarily to increasing the QRS complex up to 5-6-fold. SCH 34117 did not increase JT interval alone but enhanced a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50 μM. SCH 34117 also decreased Vmax and velocity of impulse conduction and increased excitation threshold (≥ 30 μM) while producing a negative inotropic effect (10 μM) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100 μM. In isolated rabbit ventricular myocytes, SCH 34117 (100 μM) reduced Na+ current more effectively than 100 μM loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) current to ~ ½ control value at 6 x 10^{-6} M as the concentration at which ½ current is blocked (k0.5) was 5 x 10^{-6} M (k0.5 for loratadine was 8.7 x 10^{-6}). SCH 34117 had no effect at 10^{-5} M on inward rectifier current (iK1) although the curve was flatter at 3 x 10^{-5} M; loratadine had more pronounced effect than SCH 34117. In terms of general safety pharmacology studies, SCH 34117 induced no effect on the rat gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg. SCH 34117 induced no effect on the rat renal system at oral doses up to 12 mg/kg. SCH 34117 induced no effect on the rat gastrointestinal system at oral doses up to 12 mg/kg.

Safety pharmacology conclusions: Appropriate safety pharmacology studies were performed with SCH 34117 and no significant concerns were observed. SCH 34117 has been shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K+ channels as well as a cloned human hKv1.5. In addition, all positive cardiac findings were observed during *in vitro* assessments while *in vivo* studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters. Thus, SCH 34117 is considered to be reasonably safe in this regard.

III. PHARMACOKINETICS/TOXICOKINETICS:

All pharmacokinetic/toxicokinetic studies were reviewed under IND 55,364 and NDA 21-165 except for a metabolism study with SCH 34117, which is reviewed under IND 58,506. See the attached reviews for the detailed study evaluations.

PK/TK summary: SCH 34117 was generally well absorbed with an oral bioavailability of 45-94% observed in rats and 47-57% in monkeys. Plasma concentrations of SCH 34117 increased supra-proportionally with dose in rats and drug accumulation was evident. Systemic exposure was greater in females than in males. In monkeys, plasma SCH 34117 levels increased proportionally to surpa-proportionally. Following loratadine administration, systemic exposure to SCH 34117 was greater in all species tested except for rabbits. Tmax was achieved within 4 hours in rabbits, mice and monkeys and 1.5-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. Drug accumulation was evident and no gender differences were observed. In rats, SCH 34117 was widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Distribution of ^{14}C-loratadine in pregnant rats demonstrated that radioactivity crossed the placental barrier equally at the post-embryonic period and near-term. Tissue distribution was similar in maternal and fetal tissues with lower levels found in the fetus. Plasma protein binding of SCH 34117 was variable across species as the mouse, rat, monkey and humans demonstrated 94.4%, 90.5%, 85.8% and 85.0% binding, respectively. The comparative species metabolism of SCH 34117 is summarized in Figure 1. SCH 34117 was extensively metabolized in rats, mice and monkeys and the metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products. Metabolism of SCH 34117 occurred through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position was more extensive in humans. Male rats achieved relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. In vitro studies confirmed the results of the in vivo studies and demonstrated that the hydroxylated metabolites are formed in humans although unchanged SCH 34117 was the primary compound detected. The metabolism profile of SCH 34117 is generally similar to that of loratadine with no SCH 34117-specific metabolites formed. The Desloratadine D12 Tablet degradants [redacted] were detected in male rat plasma 3 hours following oral administration of 6.5 mg ^{14}C-SCH 34117/kg. None was detected in urine samples. *In vitro* incubations of ^{14}C-SCH 34117 with Aroclor 1254-treated rat liver microsomes of S9 fractions at drug concentrations of 35 and 100 µM also demonstrated the presence of [redacted]; [redacted] was also detected in liver S9-fraction samples. Excretion of SCH 34117-related radioactivity was primarily through the feces with a large portion contributed through the bile. Approximately 20-40% was excreted through the urine.

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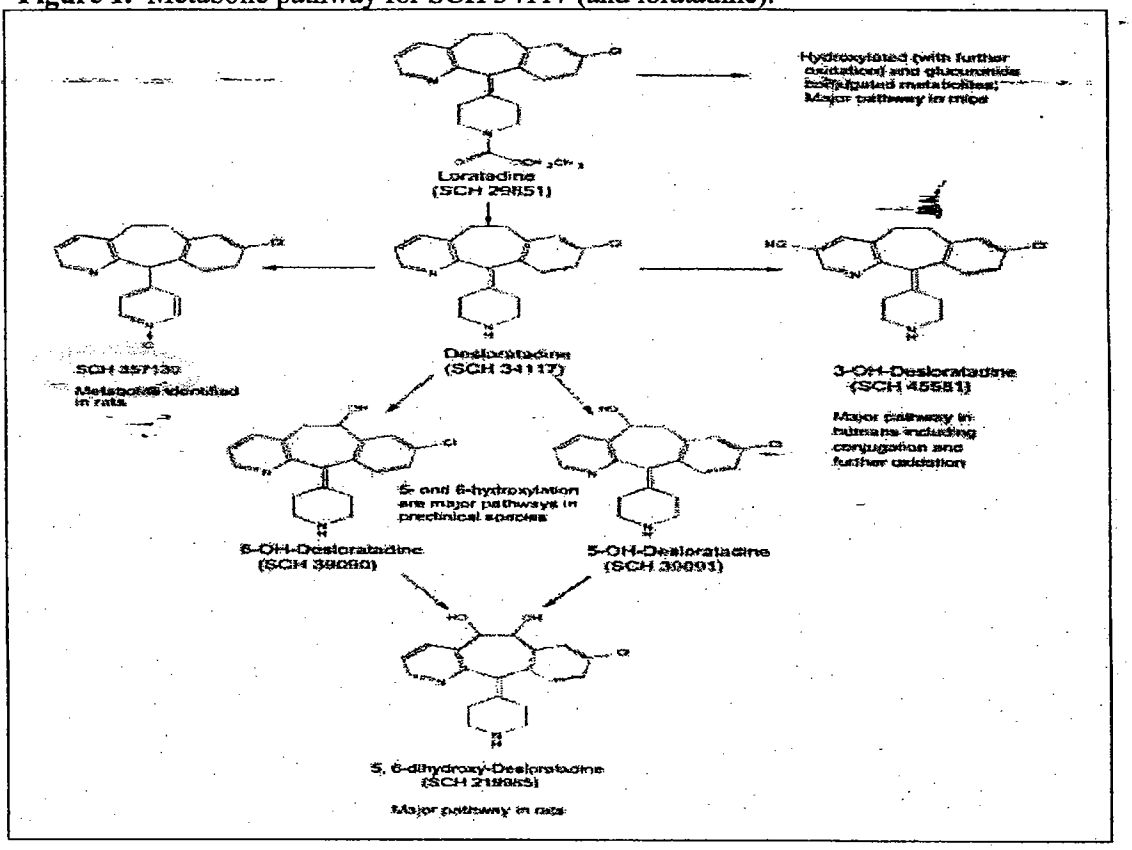
Figure 1. Metabolic pathway for SCH 34117 (and loratadine).



PK/TK conclusions: Appropriate studies were performed to assess the PK/TK of SCH 34117. Systemic exposure tended to increase supra-proportionally with increasing dose and drug accumulation was evident. SCH 34117 was widely distributed and extensively metabolized. Excretion was primarily through the feces following oral administration.

IV. GENERAL TOXICOLOGY:

All toxicology studies were reviewed under IND 55,364 and NDA 21-165 except for two 3-month oral toxicology studies in rats and monkeys performed to qualify the proposed specifications of drug product impurities . These two studies are reviewed below. See the attached reviews for the detailed study evaluations of the other studies.

Study title: Three month oral (gavage) toxicity study of SCH 34117 with degradants ,) in rats

Key study findings: The NOAELs for this study were 3 mg/kg for males and 10 mg/kg for females based upon findings related to phospholipidosis in tissues/organs throughout the body but primarily in the liver. Primary target organs include the liver, lung, and heart. The NOAEL

doses are associated with systemic exposures of 706 ng.hr/ml in males and 5510 ng.hr/ml in females. The levels of added degradants in the current formulation are greater than the proposed levels of . The identified toxicities have been observed previously with SCH 34117 and are not considered to be associated with the added degradants.

Study no: 00074
Volume #, and page #: 4.3, 1
Conducting laboratory and location: Safety Evaluation Center, Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation: July 28, 2000
GLP compliance: Yes
QA report: yes (✔) no ( )
Drug, lot #, radiolabel, and % purity: With added degradants: Without added degradants not reported
Formulation/vehicle: aqueous methylcellulose

Methods (unique aspects): Animals were dosed by oral gavage on a daily basis for 91 or 92 days
Dosing:
Species/strain: Rat/ CD[SD]IGS BR VAF/Plus
#/sex/group or time point (main study): see table below
Satellite groups used for toxicokinetics or recovery: see table below
Age: 6 weeks old at dosing initiation
Weight: 135.9-213 g at dosing initiation
Doses in administered units: see table below
Route, form, volume, and infusion rate: oral gavages, suspension, see below, NA

Group	Test/control article	Total daily dose (mg/kg)	Dose volume (ml/kg)	Dose conc. (mg/ml)	Number of rats			
					Toxicity portion		Satellite portion	
					M	F	M	F
C1	Vehicle Control	0	5	0	10	10	-	-
T1	Low dose (SCH 34117 with degradants)	3	5	0.6	10	10	12	12
T2	Mid dose (SCH 34117 with degradants)	10	5	2	10	10	12	12
T3	High dose (SCH 34117 with degradants)	30	5	6	10	10	12	12
T4	Comparative control (SCH 34117 without degradants)	30	5	6	10	10	12	12

Observations and times:
Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Pretest, weeks 3 and 13
EKG: Not assessed

Hematology:	Weeks 4 and 13
Clinical chemistry:	Weeks 4 and 13
Urinalysis:	Weeks 4 and 13
Gross pathology:	At necropsy (week 14)
Organs weighed:	At necropsy, adrenal gland, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, spleen, testes, thymus, thyroid/parathyroid, uterus
Histopathology:	Full assessment at necropsy; al organs/tissues from rats in control groups and high-dose groups, animals that died prior to schedule, all gross findings and all potential target organs.
Toxicokinetics:	Week 9, 4 sex/group/time point at 2.5, 4, and 24 hours after dosing on day 56
Other:	none

Results:

Mortality: One mid-dose male and two comparative control females were found dead on days 27, 39 and 11 and cause of death was attributed to mis-dosing of the lungs (see Table 1). A high-dose male was sacrificed on day 64 after exhibiting clinical observations of gasping, chromorhinorrhea, abnormal gait and swelling. The findings were attributed to perforation of the esophagus and associated with secondary hematology changes.

Clinical signs: No drug-related findings.

Body weights: Body weight gain was reduced in mid- and high-dose males and the comparative control group in males and females (see Table 1).

Table 1: Summary of mortality and body weight gain data.

Parameter	Dose group (mg/kg)				
	VC	3	10	30	Comparative (30)
Mortality	0M, 0F	0M, 0F	1M, 0F	1M, 0F	0M, 2F
Body weight gain (% Δ vs VC)		M: ↓3 F: ↑6	M: ↓23 F: no Δ	M: ↓30 F: ↓4	M: ↓30 F: ↓14

Food consumption: Food consumption was reduced by ~ 8-10% from weeks 7 onward in high dose animals and animals of the comparative control group.

Ophthalmoscopy: No drug-related findings.

Hematology: Increased neutrophil numbers were observed at weeks 4 and 13 (M: 51%, 33%, 27%, 105% in groups T1, T2, T3 and T4, respectively; F: 0%, 18%, 73%, 85%) and neutrophil % at week 13 (M: 34%, 29%, 34%, 56%; F: -16%, -10%, 30%, 32%). Higher numbers and increased incidence of vacuolated lymphocytes in high-dose females (both groups) were noted (8.2-9.5/100 WBC vs 0-1 in vehicle control animals).

Clinical chemistry: No drug-related findings.

Urinalysis: Increased urine volume at was noted after week 13 (M: -22%, 54%, 63%, 28% in groups T1, T2, T3 and T4, respectively; F: 43%, 84%, 114%, 161%).

Organ weights: Reduced absolute adrenal gland weight (M: 16, 17, 23, 21%; F: 4, 112, 4, 14% in groups T1, T2, T3 and T4, respectively), increased absolute and relative liver weight (M: 9, 8, 24, 25% and 10, 17, 41, 44%; F: 10, 5, 10. 9% and 8, 7, 16, 21% in groups T1, T2, T3 and T4, respectively), increased absolute and relative lung weight (F: 3, 0, 24, 21% and 2, 2, 36, 29% in groups T1, T2, T3 and T4, respectively), reduced thymus absolute weight (M: 9, -7, -18, -27%; F: -5, -5, -22, -36% in groups T1, T2, T3 and T4, respectively) and increased absolute (6, 6, 29, 13%) and relative uterus weight (4, 13, 37, 21%) were noted.

Gross pathology: Gross findings, summarized in Table 2, with a dose-related increase in incidence were noted in the adrenal glands (small), lungs (discoloration, adhesion), liver (enlarged, lobular pattern) and uterus (dilatation).

Table 2: Summary of gross pathology data.

Findings	Males					Females				
	C1	T1	T2	T3	T4	C1	T1	T2	T3	T4
Adrenal glands - small	0	0	0	1	0	0	0	0	0	0
Liver										
Enlarged	0	1	0	2	2	0	0	0	0	0
Accentuated lobular pattern	0	0	0	0	2	0	0	0	0	0
Lung										
Discoloration, diffuse, red	0	0	0	0	0	0	0	0	2	1
Discoloration, localized, red	0	0	0	0	1	0	0	0	0	0
Discoloration, mottled, red	0	0	1	0	0	0	0	0	0	1
Discoloration	0	0	0	0	0	0	0	0	0	1
Adhesion	0	0	0	0	1	0	0	0	0	0
Uterus – dilatation, generalized						1	2	2	4	1

Histopathology: The primary histopathologic findings were related to phospholipidosis and included vacuoaltion, atrophy and necrosis in tissues/organs throughout the body but primarily in the liver (Table 3). Other findings of note include pulmonary inflammation, cardiac myofiber degeneration.

Table 3: Summary of microscopic pathology data.

Findings	Males					Females				
	C1	T1	T2	T3	T4	C1	T1	T2	T3	T4
Bone marrow (# examined)	10		1	10	10	10			10	10
Hyperplasia, myeloid –										
Minimal	0		0	0	1	0			0	0
Fibrosis - minimal	0		0	1	0	0			0	0
Epididymides	10		10	10	10					
Cell debris, luminal										
Minimal	0		0	1	1					
Vacuolation, epithelium										
minimal	0		0	4	5					
Esophagus	10		1	10	10	10		10	10	10
Vacuolation, myofiber										
minimal	0		0	0	0	0		0	2	1

Eyes	10		1	10	10	10	10	10	10	10
Mineralization, corneal										
minimal	0		0	0	3	0	0	0	0	0
Heart	10		1	10	10	10		10	10	10
Degeneration, myofiber, focal										
Minimal	0		0	0	2	1		1	0	0
Kidneys	10	1	1	10	10	10	1	10	10	10
Single cell necrosis, tubular										
Minimal	0	0	0	0	1	0	0	0	0	0
Cell infiltration, mononuc cell										
Minimal	0	1	0	1	0	1	0	1	0	2
Tubular basophilia										
Minimal	3	0	1	6	4	0	0	0	0	1
Liver	10	10	10	10	10	10		10	10	10
Vacuolation, midzonal, hepatoce										
Minimal										
Mild	0	0	4	5	7	0		0	0	0
Vacuolation, biliary, focal	0	0	0	3	3	0		0	0	0
Minimal										
Mild	0	0	0	0	0	0		0	6	7
Hypertrophy, centrilobular	0	0	0	0	0	0		0	4	1
Minimal										
Mild	0	0	3	2	3	0		0	5	7
Moderate	0	0	0	6	4	0		0	0	1
	0	0	0	2	3	0		0	0	0
Lungs	10		1	10	10	10		10	10	10
Vacuolation, alv. macrophage										
Minimal	0		0	0	0	0		0	2	5
Mild	0		0	0	0	0		0	6	1
Necrosis, mucosal										
Mild	0		0	0	0	0		0	0	1
Hypertrophy, medial										
Mild	0		0	0	0	0		0	0	1
Hyperplasia, epithelial										
Mild	0		0	0	1	0		0	0	0
Hemorrhage, alveolar										
Minimal	0		0	0	0	0		0	0	2
Fibrosis, lumen, bronchial										
Minimal	0		0	2	0	0		0	0	0
Mild	0		0	1	1	0		0	1	0
Fibrosis, pleural – mild	0		0	0	1	0		0	0	0
Eosinophilia, alveolar wall										
Mild	0		0	0	0	0		0	0	2
Congestion										
Minimal	0		0	0	1	0		0	0	0
Mild	0		0	0	0	0		0	0	2
Moderate	0		1	0	0	0		0	0	0
Ovaries						10		10	10	10
Vacuolation, corpora lutea										
Minimal						0		0	1	1
Degeneration, corpora lutea										
Minimal						0		0	3	2
Pancreas	10		1	10	10	10		10	10	10
Vacuolation, ductular										
Minimal	0		0	0	0	0		0	2	2
Mild	0		0	0	0	0		0	0	2

Stomach	10	1	10	10	10	1	10	10	10
Vacuolation, epithelium									
Minimal	0	0	0	0	0	0	0	3	1
Thymus	10	1	10	10	10			10	10
Atrophy, lymphoid									
Minimal	0	0	1	0	0			0	0
Mild	0	0	1	0	0			0	0
Trachea	10	1	10	10	10		10	10	10
Vacuolation, epithelium									
Minimal	0	0	0	0	0		0	2	0
Necrosis, mucosal									
Mild	0	0	0	0	0		0	0	1
Metaplasia, epithelium									
mild	0	0	0	0	0		0	1	0
Uterus					10	2	10	10	10
Vacuolation, endometrium, macrophage									
Minimal					0	0	0	1	1
Vacuolation, epithelium									
mild					0	0	0	0	1

Toxicokinetics: Systemic exposure increased supra-proportionally in both males and females with increasing dose (Table 4). Exposure in females was 1.2-2.2-fold greater than in males. Tmax was comparable between genders and ranged from 2.5 to 4 hours.

Table 4: Summary of toxicokinetic data following dosing on day 56.

		TK Parameter		
Dose group	Gender	AUC (0-24 hr) (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)
T1 (3 mg/kg)	Male	706	59.3	2.5
	Female	1580	154	2.5
T2 (10 mg/kg)	Male	3390	268	4
	Female	5510	436	4
T3 (30 mg/kg)	Male	16600	1160	4
	Female	19700	1080	2.5
T4 (30 mg/kg w/o degradants)	Male	14100	940	4
	Female	25300	1290	2.5

Summary of individual study findings: The NOAEL for this study was identified as 3 mg/kg for males and 10 mg/kg for females based upon findings related to phospholipidosis in tissues/organs throughout the body but primarily in the liver. Primary target organs include the liver, lung, and heart. The NOAEL doses are associated with systemic exposures of 706 ng.hr/ml in males and 5510 ng.hr/ml in females. A previous 3-mos study in rats (3, 30, 60, 120 mg/kg) resulted in a NOAEL of 3 mg/kg for females and 30 mg/kg for males. Liver vacuolation was noted at doses of 60 mg/kg or greater. Epididymal and thymic vacuolation were noted at 30 mg/kg so the NOAEL could be lowered to 3 mg/kg in males. The results of the current study suggest that the NOAEL in females could be increased to 10 mg/kg. The levels of added

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degradants in the current formulation are greater than the proposed levels of . The identified toxicities have been observed previously with SCH 34117 and are not considered to be associated with the added degradants.

Study title: Three month oral (gavage) toxicity study of SCH 34117 with degradants ,) in cynomolgus monkeys

Key study findings: A NOAEL of 12 mg/kg was identified due to histopathologic changes associated with systemic phospholipidosis (vacuolation, atrophy). Primary target organs included the lung, thymus, adrenal gland, liver and kidney. The NOAEL is associated with systemic exposure levels of 6741 ng.hr/ml in males and 12999 ng.hr/ml in females. Levels of added degradants are greater than the proposed levels of (

Study no: 00208
Volume #, and page #: 4.6, 1
Conducting laboratory and location: Safety Evaluation Center, Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation: August 2, 2000
GLP compliance: Yes
QA report: yes (✔) no ( )
Drug, lot #, radiolabel, and % purity: Added degradants: ; without added degradants not reported
Formulation/vehicle aqueous methylcellulose

Methods (unique aspects)**:** Animals were dosed by oral gavage on a daily basis for 91 to 93 days
Dosing:

Species/strain: cynomolgus monkeys
#/sex/group or time point (main study): see table below
Satellite groups used for toxicokinetics or recovery: none
Age: stated as juvenile/young adult
Weight: 2.1-4.4 kg at dosing initiation
Doses in administered units: see table below
Route, form, volume, and infusion rate: oral gavage, suspension, see below, NA

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Group	Test/control article	Total daily dose (mg/kg)	Dose volume (ml/kg)	Dose conc. (mg/ml)	Number of monkeys/sex
C1	Vehicle Control	0	5	0	4
T1	Low dose (SCH 34117 with degradants)	6	5	1.2	4
T2	Mid dose (SCH 34117 with degradants)	12	5	2.4	4
T3	High dose (SCH 34117 with degradants)	24	5	4.8	4
T4	Comparative control (SCH 34117 without degradants)	24	5	4.8	4

Observations and times:

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Daily
Ophthalmoscopy:	Pretest, weeks 3 and 13
EKG:	Twice pretest, weeks 4 and 13; 3-5 hours after dosing
Hematology:	Twice pretest, Weeks 4 and 12
Clinical chemistry:	Twice pretest, Weeks 4 and 12
Urinalysis:	Twice pretest, Weeks 4 and 12
Gross pathology:	At necropsy (week 14)
Organs weighed:	At necropsy, adrenal gland, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, spleen, testes, thymus, thyroid/parathyroid, uterus
Histopathology:	Full assessment at necropsy; all organs/tissues from rats in control groups and high-dose groups, animals that died prior to schedule, all gross findings and thymus and lungs from all other groups.
Toxicokinetics:	Week 9, 4 sex/group/time point at 1.5, 4, and 24 hours after dosing on day 56; assay LOQ of
Other:	Physical exam (body temperature, heart rate and blood pressure): Twice pretest, weeks 4 and 13

Results:

Mortality: No deaths occurred.

Clinical signs: Emesis unrelated to dosing procedure was noted in 1-3 animals in the mid and high-dose groups. Abnormal loose stool was also noted in two high-dose males. One of these high-dose males exhibited abdominal distension.

Body weights: No drug-related findings were noted.

Food consumption: No drug-related findings were noted.

Ophthalmoscopy: No drug-related findings were noted.

Physical Examination: No drug-related findings were noted.

Electrocardiogram: One high-dose (T3) male exhibited increased QRS interval (50/51 at weeks 4/12 vs 21-27 pre-dosing). Increased QT interval in the same male (155-179 at weeks 4/12 vs 137 pre-dose). This male also demonstrated an increased QTc interval (240-274 ms vs 220-228 ms). T4 females exhibited an increased PR interval (up to 25 ms). The consulting cardiologist concluded that there were no test article related findings.

Hematology: Decreased reticulocyte % (14%, 19%, 49%, 32%) in males and increased reticulocyte % in females (8%, 2%, 36%, 24%) were noted in group T1, T2, T3 and T4, respectively. Increased platelet numbers (26-49%) were observed in treated males. An increased number of vacuolated lymphocytes were noted in drug-treated animals (1.5-5.7/100 WBC) while none were observed in vehicle control animals.

Clinical chemistry: No drug-related findings were noted.

Urinalysis: No drug-related findings were noted.

Organ weights: Absolute thymus weight in males was decreased by 69% and 38% in the T3 and T4 groups. Similar changes were observed with relative (to body weight) thymus weight. Absolute lung weight in males was increased by 23% in the comparative control group (T4).

Gross pathology: Gross findings with a dose-related increase in incidence, summarized in Table 5, were noted in the large intestine, liver, lungs, parathyroid and spleen.

Table 5: Summary of gross pathology data.

Findings	Males					Females				
	C1	T1	T2	T3	T4	C1	T1	T2	T3	T4
Large intestine										
Distention, gaseous, segmental	0	0	0	1	1	0	0	0	3	1
Liver										
Accentuated lobular pattern	0	0	0	1	1	0	0	0	0	2
Discoloration, focal, red	0	0	0	1	0	0	0	0	0	0
Lung										
Discoloration, focal, tan	0	0	0	0	0	0	0	0	1	0
Discoloration, mottled, tan	0	0	0	1	0	0	0	0	0	0
Parathyroid – enlarged, unilateral	0	0	0	0	1	0	0	0	0	0
Spleen – altered texture	0	0	0	0	1	0	0	0	0	0

Histopathology: Primary findings were associated to phospholipidosis and included vacuoaltion, atrophy and macrophage accumulation in various tissues (see Table 6). Findings were generally of minimal to mild severity. Thymic atrophy was associated with decreased organ weight and pulmonary macrophage accumulation was associated with increased lung weight. No definitive differences were note between the dose group with added degradants and the group without added degradants (T4).

Table 6: Summary of microscopic pathology data.

Findings	Males					Females				
	C1	T1	T2	T3	T4	C1	T1	T2	T3	T4
Adrenal gland (# examined)	4			4	4	4			4	4
Vacuolation,cytoplasmic, zona fasciculata										
minimal	0			0	0	0			0	1
Heart - Cell infiltrat, myocardial	4			4	4	4		1	4	4
Minimal	0			0	0	0		0	2	1
Kidneys	4			4	4	4			4	4
Cell infiltration, mononuc cell										
Minimal	0			0	1	0			1	0
Vacuolation, medullary										
Minimal	0			0	1	0			0	0
Liver	4			4	4	4			4	4
Vacuolation, midzone, periport										
Minimal	0			0	0	0			1	0
Lungs	4	4	4	4	4	4	4	4	4	4
Accumulation,Macrophage, multifocal										
Minimal	0	0	0	1	3	0	0	0	2	3
Mild	0	0	0	1	0	0	0	0	0	1
Metaplasia, bronchiolo-alv, subpleural										
mild	0	0	0	0	0	0	0	0	1	0
Spleen - Fibrosis, capsular, focal	4			4	4	4			4	4
Minimal	0			0	1	0			0	0
Thymus	4	4	4	4	4	4	4	4	4	4
Atrophy, lymphoid										
Minimal	0	0	1	0	3	1	0	0	0	2
Mild	0	0	0	1	0	0	0	0	0	1
Moderate	0	0	0	1	0	0	0	0	0	0

Toxicokinetics: Systemic exposure increased proportionally in both males and females with increasing dose (Table 7). Exposure in females was 1.1- to 2.0-fold greater than in males. Exposure in females was ~ 2-fold greater with the formulation without added degradants than with the formulation with added degradants. Tmax was comparable between genders and ranged from 2.5 to 4 hours. This range supports the timing of the electrocardiograms.

Table 7: Summary of toxicokinetic data following dosing on day 56.

Dose group	Gender	AUC (0-24 hr) (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)
T1 (6 mg/kg)	Male	4825	281	4
	Female	5290	294	4
T2 (12 mg/kg)	Male	6741	418	3.4
	Female	12999	743	3.4
T3 (24 mg/kg)	Male	16702	921	2.75
	Female	18707	1004	3.4
T4 (24 mg/kg w/o degradants)	Male	18492	929	4
	Female	36784	1695	3.2

of the impurities in the drug product (see the chemistry consult). It was concluded that, while the 3-month toxicology studies support the proposed doses on a mg/kg basis, structural alerts identified on each impurity necessitate that the sponsor provide further genotoxic qualification studies to support the proposed levels or lower the specifications to less than 0.1% in the drug product.

Chronic Toxicity: The similar toxicological findings following SCH 34117 and loratadine administration in the 3 month rat and monkey studies at similar exposure levels of SCH 34117 support bridging to the chronic loratadine toxicology program. Therefore, the Sponsor was not required to perform chronic toxicity studies with SCH 34117.

Pseudoephedrine sulfate: No nonclinical studies have been performed for pseudoephedrine sulfate. There is, however, extensive clinical experience with this compound and it is approved for use in the indicated population in combination with loratadine, the parent compound of desloratadine.

Toxicology conclusions: The nonclinical safety of SCH 34117 has been adequately tested with the primary finding related to phospholipidosis. However, the safety of the combination of desloratadine and PSE has not been assessed in a general toxicology study. The sponsor was previously informed that a 3-month general toxicology study in one species using the desloratradine/PSE combination would be needed for bridging purposes if desloratdine is not a marketed product. The original NDA for desloratadine (NDA 21-165) is currently considered to be Approvable.

V. GENETIC TOXICOLOGY:

All genetic toxicology studies were reviewed under IND 55,464 and NDA 21-165 with the exception of a bacterial reverse mutation assay and an in vivo mouse micronucleus assay performed to qualify the proposed specifications of four drug product impurities [redacted]. These two studies are reviewed below. See the attached reviews for the detailed study evaluations of the other studies. See the attached reviews for the detailed study evaluations.

Study title: *Salmonella-Escherichia*/Mammalian-microsome reverse mutation assay with a confirmatory assay of SCH 34117 with degradants [redacted]

Key findings: SCH 34117 with added degradants [redacted] tested negatively in the reverse mutation assay. However, this assay does not adequately address the mutagenic potential of the degradants since structural alerts were identified with these added compounds. Thus, the mutagenic potential of

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Summary of individual study findings: A NOAEL of 12 mg/kg was identified due to histopathologic changes associated with systemic phospholipidosis (vacuolation, atrophy). Primary target organs included the lung, thymus, adrenal gland, liver and kidney. The NOAEL is associated with systemic exposure levels of 6741 ng.hr/ml in males and 12999 ng.hr/ml in females. This NOAEL dose is consistent with that of a previous 3-mos study (6, 12, 18/24 mg/kg). The levels of added degradants are greater than the proposed levels of

Toxicology summary:

Acute Toxicity: Acute, oral and intraperitoneal studies in mice and rats, as well as an oral study in monkeys were submitted to IND 55,364. Maximum nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS and respiratory system in rats and mice and the gastrointestinal system in monkeys.

Subchronic Toxicity: Studies were conducted in rats and monkeys for up to 3 months duration with both SCH 34117 and loratadine in order to support a bridging strategy to the loratadine chronic toxicology program. The primary toxicity findings in both species, similar to loratadine, was systemic phospholipidosis in organ systems throughout the body. The kidney and epididymides were target organs in rats.

In rats, treatment-related mortality occurred at a dose of 240 mg/kg SCH 34117 in one of two 2-week studies and at a dose of 120 mg/kg in males and 30 mg/kg or greater in females in a three month study. Systemic phospholipidosis was the primary toxicity finding in tissues throughout the body. In addition, kidney necrosis and luminal cellular debris of the epididymides were observed following 3-month administration. The toxicity profile of SCH 34117 was similar to that of the active control (loratadine) group. However, loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. The NOAEL in the 3-month toxicity study was 3 mg/kg in females and 30 mg/kg in males. These doses resulted in mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 1890 ng.hr/ml and 9490 ng.hr/ml in females and males, respectively.

In monkeys, no treatment-related mortality was observed at doses up to 18 mg/kg for 3 months. Systemic phospholipidosis was again the primary toxicity finding in organs/tissues throughout the body. The toxicity profiles observed in SCH 34117-treated groups were comparable to the active (loratadine) control group at similar SCH 34117 systemic exposure levels. The NOAEL in the 3-month toxicity study was 12 mg/kg which resulted in mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 21613 ng.hr/ml.

Additional three-month oral toxicology studies in rats and monkeys were performed for the purpose of qualifying proposed drug product specifications for degradants. The studies resulted in comparable toxicity profiles to previous 3-month studies performed for IND 55,364 indicating that the degradants produced no additional toxicity at the levels tested. A consult from the chemistry reviewer was requested to provide a safety assessment of the proposed levels

the degradants should be tested individually at the limit doses for each individual compound for the purpose of qualification.

Study no:
Study type: Bacterial mutagenicity, plate incorporation
Volume #, and page #: 6, 1
Conducting laboratory and location:
Date of study initiation: October, 2000
GLP compliance: Yes
QA reports: yes (✔) no ( )
Drug, lot #, radiolabel, and % purity: SCH 34117 with added degradants:

Formulation/vehicle: Dissolved in DMSO

Methods:

Strains/species/cell line: *Salmonella typhimurium* TA98, TA100, TA1535, TA97a and TA102. *Escherichia coli* WP2*uvr*A

Dose selection criteria:

Basis of dose selection: Results of a previous bacterial mutagenicity study of SCH 34117 (SN 97027).

Range finding studies: not performed

Test agent stability: SCH 34117 determined to be stable in DMSO for up to 4 hours under ambient temperatures and light conditions at concentrations of 0.01 and 60 mg/ml and for up to 36 days at approximately –20 degrees C at 0.01 and 50 mg/ml.

Metabolic activation system: liver microsomal enzymes (S9 homogenate; 36.8-40.8 mg protein per ml) prepared from male SD rats injected with Aroclor 1254 (200 mg/ml in corn oil) at 500 mg/kg.

Controls:

Vehicle: DMSO

Negative controls: DMSO

Positive controls: see table below

Tester strain	S9 mix	Positive control	Concentration (µg/plate)
TA98	+	Benzo[a]pyrene	2.5
	-	2-nitrofluorene	1
TA100	+	2-aminoanthracene	2.5
	-	sodium azide	2
TA1535	+	2-aminoanthracene	2.5
	-	sodium azide	2
TA97a	+	2-aminoanthracene	2.5
	-	ICR-191	2
TA102	+	2-aminoanthracene	15
	-	mitomycin C	1
WP2uvrA	+	2-aminoanthracene	25
	-	4-nitroquinoline-N-oxide	1

Comments: selected controls are mostly adequate; is mitomycin C appropriate negative control for TA102

Exposure conditions: The assay was performed in two trials.

Incubation and sampling times: 52 hour incubation; sampled immediately after incubation period

Doses used in definitive study: Trial 1:

Tester strain	Non-activation (µg/plate)	Concentration (µg/plate)
TA98	15.6, 31.3, 62.5, 125, 250, 500, 1000	15.6, 31.3, 62.5, 125, 250, 500, 1000
TA100	7.8, 15.6, 31.3, 62.5, 125, 250, 500	7.8, 15.6, 31.3, 62.5, 125, 250, 500
TA1535	15.6, 31.3, 62.5, 125, 250, 500, 1000	47, 94, 188, 375, 750, 1500, 3000
TA97a	1.95, 3.9, 7.8, 15.6, 31.3, 62.5, 125	1.95, 3.9, 7.8, 15.6, 31.3, 62.5, 125
TA102	3.9, 7.8, 15.6, 31.3, 62.5, 125, 250	7.8, 15.6, 31.3, 62.5, 125, 250, 500
WP2uvrA	47, 94, 188, 375, 750, 1500, 3000	47, 94, 188, 375, 750, 1500, 3000

Doses used in definitive study: Trial 2 (based on results of Trial 1)

Tester strain	Non-activation (µg/plate)	Concentration (µg/plate)
TA98	15.6, 31.3, 62.5, 125, 250, 500, 1000	15.6, 31.3, 62.5, 125, 250, 500, 1000
TA100	7.8, 15.6, 31.3, 62.5, 125, 250, 500	7.8, 15.6, 31.3, 62.5, 125, 250, 500
TA1535	15.6, 31.3, 62.5, 125, 250, 500, 1000	47, 94, 188, 375, 750, 1500, 3000
TA97a	15.6, 31.3, 62.5, 125, 250, 500, 1000	15.6, 31.3, 62.5, 125, 250, 500, 1000
TA102	3.9, 7.8, 15.6, 31.3, 62.5, 125, 250	7.8, 15.6, 31.3, 62.5, 125, 250, 500
WP2uvrA	47, 94, 188, 375, 750, 1500, 3000	47, 94, 188, 375, 750, 1500, 3000

Study design: Tester strains were exposed via the plate incorporation method in two trials. A third trial was performed with strain TA97 since the high dose in the initial trial did not induce cytotoxicity. Seven doses tested in trial 1.

Analysis:

No. of replicates: triplicate

Counting method: The number of revertant colonies per plate for negative controls and drug-treated samples were counted manually. An automated colony counter counted positive controls.

Criteria for positive results: At least a 2-fold (for strains TA98, TA100, TA97a, TA102 and WP2uvrA) or 3-fold (for strain TA1535) increase in mean revertants per plate of at least one tester strain over the mean revertants per plate of appropriate vehicle control.

This increase had to be accompanied by a dose response to increasing concentrations of test article.

Summary of individual study findings:

Study validity: The assay was carried out in a valid fashion to determine the mutagenic potential of SCH 34117. However, the mutagenic potential of the degradants was not adequately tested since the presence of structural alerts on the structures suggests that each degradant should be tested to its own limit dose. Trial 1 demonstrated cytotoxicity at the high doses tested in all strains except for strain TA97a.

Study outcome: In Trial 1, no increase in mean revertants per plate was noted with any tester strain in the presence or absence of S9 mix. Cytotoxicity was not noted at the highest doses tested with strain TA97A. Trial 2 and Trial 3 (with strain TA97a) resulted in no increase in mean revertants per plate was noted with any tester strain in the presence or absence of S9 mix. Thus, SCH 34117 with added levels of selected

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degradants [redacted] tested negatively in this assay. This conclusion is in agreement with the sponsor's conclusion.

Study title: Mouse bone marrow erythrocyte micronucleus study of SCH 34117 with degradants [redacted]

Key findings: SCH 34117 with added degradants [redacted] tested negatively in this mouse bone marrow erythrocyte micronucleus study. However, this assay does not adequately address the genotoxic potential of the degradants since structural alerts were identified with these compounds. Thus, the mutagenic potential of the compounds should be tested individually at the limit doses for each individual compound for the purpose of qualifying these compounds. Dosing in females could likely have been increased since only minimal toxicity was noted in high-dose females.

Study no: [redacted]
Study type: In vivo mouse micronucleus
Volume #, and page #: 6, 87
Conducting laboratory and location: [redacted]
Date of study initiation: October, 2000
GLP compliance: Yes
QA reports: yes (✔) no ( )
Drug, lot #, radiolabel, and % purity: SCH 34117 with [redacted] added degradants: [redacted]
Formulation/vehicle: [redacted] aqueous methylcellulose

Methods:

Strains/species/cell line: Mouse [redacted]); 6-8/sex/dose group
Dose selection criteria:
Basis of dose selection: Results of a previous micronucleus assay in mice study of SCH 34117 (SN 97118).
Range finding studies: not performed
Test agent stability: SCH 34117 determined to be homogenous and stable for at least 8 days under ambient conditions.
Metabolic activation system: Not applicable
Controls:
Vehicle: [redacted] aqueous methylcellulose
Negative controls: [redacted] aqueous methylcellulose
Positive controls: cyclophosphamide
Comments: selected controls are adequate

Exposure conditions: Mice received two consecutive daily ip doses.
Incubation and sampling times: 24 and 48 hours after sampling following last dose

Doses used in definitive study:

Dose group	Dose (mg/kg/da	# of mice/sex	
		24 hours	48 hours
Veh Control	0	6	6
Low	12.5	6	6
Mid	25	6	6
High	50	8	8
Pos Control	50	6	
	40		6

Study design: Five mice/sex from each dose group were sacrificed. Bone marrow erythrocytes were removed from the femur. Two bone marrow smears were prepared. For each mouse, 2000 PCE were screened for micronuclei. The micronucleus frequency of each dose was calculated from the total number of micronucleated PCE in approximately 10000 PCE pooled from five mice. Bone marrow toxicity was evaluated by the PCE/NCE ratio from at least 200 PCE in each mouse. Micronucleated NCEs were also scored during the screening of micronuclei in 2000 PCE in each mouse.

Analysis:

No. of replicates: duplicate

Counting method: Micronucleated erythrocytes were counted under a fluorescent microscope.

Criteria for positive results: A statistically significant increase of micronuclei frequency in PCE at any dose tested compared to the vehicle control group; cpmpared by ANOVA and Dunnett's t-test.

Summary of individual study findings:

Study validity: The assay was carried out in a valid fashion to determine the clastogenic potential of SCH 34117. However, dosing in females could have been higher since the only observed toxicities at the high dose included rough haircoat, squinted eyes and slight hypoactivity. Also, the clastogenic potential of the degradants was not adequately tested since the presence of structural alerts on the structures suggests that each degradant should be tested to its own limit dose.

Study outcome: No mortality occurred at 24 hours after dose administration. One high-dose male died two days after dose administration. Clinical signs included slight hypoactivity, rough haircoat and squinted eyes in high-dose animals after 24 hours and in mid- and high-dose animals after 48 hours. Bone marrow toxicity was noted at the high dose at 24 hours in both genders and in females at 48 hours. No statistically significant increase of micronucleus frequency was observed at any test article-dose group. The positive control produced an expected increase in micronucleus frequency. Thus, under the conditions tested, SCH 34117 with added degradants did not induce an increase in micronuclei frequency. This conclusion is in agreement with the sponsor's conclusion. However, dosing could likely be increased in females and the degradants should be tested individually at their limit doses to adequately assess the genotoxic potential of the degradants.

Genetic toxicology summary: The sponsor performed a bacterial reverse mutation assay and an in vivo mouse micronucleus assay using SCH 34117 with added levels of degradants for the purpose of qualifying the sponsor's proposed specifications for the added degradants. Both assays were negative under the conditions tested, similar to previous assays with SCH 34117, although dosing in the micronucleus assay in females could likely have been increased since only minimal toxicity was observed. However, these studies do not support qualification of the proposed degradant specifications since the reviewing chemist has identified structural alerts associated with these substances. Thus, to adequately qualify the proposed specifications, the sponsor should test each substance individually up to the limit dose for each substance.

Genetic toxicology studies assessing SCH 34117 were submitted to IND 55,364 and included a bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay using human lymphocytes and an *in vivo* mouse bone marrow erythrocyte micronucleus assay. SCH 34117 was negative under the conditions tested in each of the assays.

Genetic toxicology conclusions: SCH 34117 was negative in the genetic toxicology standard battery of tests. A bacterial reverse mutation assay and an in vivo mouse micronucleus assay performed using SCH 34117 with added levels of degradants were negative but do not support the qualification of the proposed specification levels for the degradants since structural alerts were identified with these substances. In order to qualify the proposed specification levels, the sponsor should perform genotoxic assessment using isolated substance up to their limit dose. Otherwise, the proposed specifications should be reduced to below in the drug product.

Labeling recommendations: The label should state that SCH 34117 tested negatively in the assays performed for the standard battery. The recommended labeling for SCH 34117 should not be changed based upon the results of the above two studies.

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VI. CARCINOGENICITY:

Carcinogenicity summary: Carcinogenicity studies have not been performed with SCH 34117. A two-year study in rats and an eighteen-month study in mice performed with loratadine induced hepatic carcinogenicity in male mice and male and female rats. In addition, the mouse study was not considered to have achieved the maximum tolerated dose (MTD). The sponsor requested a waiver from performing carcinogenicity studies with SCH 34117 under NDA 21-165 based upon SCH 34117 exposure ratios achieved during carcinogenicity studies performed with loratadine. CDER's Pharmacology/Toxicology Senior Policy Team considered the waiver request and concluded that the rat carcinogenicity study performed with loratadine sufficiently assesses the carcinogenic liability of SCH 34117 since the study resulted in an unbound DCL-derived rodent to human exposure multiple exceeding a factor of 25. However, the waiver for the mouse carcinogenicity study was not acceptable since appropriate SCH 34117 exposure multiples were not achieved in the carcinogenicity study with loratadine and the mouse study was not considered to have achieved an appropriate high dose. Thus, the sponsor was informed that a two-year mouse carcinogenicity study would be required. The Senior Policy Team felt that the study could be performed as a Phase 4 commitment since loratadine is an approved drug product and a significant portion of the population is already exposed to its metabolite SCH 34117, the genotoxicity studies for SCH 34117 resulted in negative findings and the carcinogenic potential has at least been partially assessed in the studies performed in rats and mice with loratadine. A study protocol was submitted by the sponsor for CAC concurrence and the Executive CAC provided concurrence with changes in the proposed dose selection (see Exec CAC minutes dated August 3, 2000).

Carcinogenicity conclusions: A two-year study in rats and an eighteen-month study in mice performed with loratadine induced hepatic carcinogenicity in male mice and male and female rats. The two year carcinogenicity study performed in rats using loratadine under NDA 19-658 is considered to be adequate to assess the carcinogenic potential in this species. However, a two-year mouse carcinogenicity study in mice using SCH 34117 should be performed as a Phase 4 commitment. The sponsor should submit the final study report within three years of the approval of NDA 21-165 or study initiation, whichever occurs first.

Labeling Recommendations: The label should reflect the findings stated in the carcinogenicity section of the label for loratadine with relevant animal to human dose ratios. Once the Phase 4 mouse carcinogenicity study is submitted and reviewed, the label should be updated to reflect the new information.

Addendum/appendix listing: None

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VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

All toxicology studies for SCH 34117 were reviewed under IND 55,464 and NDA 21-165. See the attached reviews for the detailed study evaluations.

Reproductive and developmental toxicology summary: Effects of SCH 34117 on fertility were studies in both sexes. In females, oral doses up to 24 mg/kg (~ 560 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) did not influence fertility although preimplantation loss was increased and numbers of implantation sites and fetuses were decreased at this dose. In males, oral doses of 12 mg/kg (~ 180 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater reduced fertility (24-64%). A dose of 3 mg/kg (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no effect on fertility. General findings in males included reduced organ weights at the high-dose (prostate, testis, epididymis; 19-42%), small and soft testes at all doses, and microscopic findings at all doses (atrophy and degeneration of the seminiferous tubules, spermatid giant cells, spermatic cellular debris and oligospermia, reduced sperm numbers, production and motility at the mid- and high-doses). The number of implantation sites and viable embryos were reduced in females mated with mid- and high-dose males and the incidence of preimplantation loss was increased. The findings in males were generally non-reversible.

Embryo-fetal development studies were performed in rats and rabbits. Oral administration at doses up to 48 mg/kg/day (~ 870 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) in rats and 60 mg/kg/day (~ 230 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) in rabbits during the period of organogenesis produced no evidence of teratogenicity. Skeletal variations in rat fetuses (unossified/reduced ossification of vetebra, sternebra and proximal phalanges) and reduced fetal body weight observed at a dose of 24 mg/kg (~ 560 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater were attributable to maternal toxicity (reduced body weight gain; 56-92% and food intake; up to 53%). No evidence of toxicity was observed at the next lowest dose tested, 6 mg/kg (~ 140 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose).

An oral peri- and post-natal study was performed in rats. A dose of 3 mg/kg SCH 34117 (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no toxicologically significant effects on F_1 pup survival, pre-weaning growth or F_1 development. A dose of 9 mg/kg (~ 190 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater led to reduced fetal weight (8-12%) and a dose-related effect on righting reflex. No significant effects were observed in the F_2 generation at doses up to 24 mg/kg (~ 520 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose).

Reproductive and developmental toxicology conclusions: SCH 34117 induced a male-specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes at an oral dose of 12 mg/kg. An increase in pre-implantation and decreased number of implantations and fetuses were noted in female rats; reduced body weight and slow righting reflex were noted in pups. SCH 34117 was not teratogenic at oral doses up to 48 mg/kg.

The sponsor was previously informed that a teratology study in one species using the desloratadine/PSE combination would be needed for bridging purposes if desloratadine is not a marketed product. The original NDA for desloratadine (NDA 21-165) is currently considered to be Approvable.

Labeling recommendations: The Pregnancy Category for the label should be "C" due to the adverse fetal effects described above.

VIII. SPECIAL TOXICOLOGY STUDIES:

No special toxicology studies were performed with desloratadine.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: With the exception of a metabolism study, two 3-month oral toxicology studies in rats and monkeys and two genetic toxicology assays, all nonclinical studies were submitted and reviewed in IND 55,364 or NDA 21-165. The toxicology profile for SCH 34117, the primary active metabolite of loratadine, from studies of up to 3 months duration was comparable to that of loratadine. The primary finding was phospholipidosis in tissues/organs throughout the body. Additional 3-month toxicology studies in rats and monkeys were performed for the purpose of qualifying degradants and resulted in no additional adverse findings. Therefore, chronic studies with SCH 34117 were not required. SCH 34117 tested negatively in the standard battery of genetic toxicology assays. Two additional assays were performed for the purpose of qualifying degradants and resulted in negative findings. However, these studies do not support the proposed specifications since the degradants are considered structural alerts and each need to be tested to the limit dose in each assay. Carcinogenicity studies with SCH 34117 have not been performed. However, a 2-year rat assay with loratadine is considered to be adequate to assess the carcinogenic potential of SCH 34117 in rats. The sponsor committed to perform a 2-year assay in mice using SCH 34117 as a Phase 4 commitment since an 18-month assay with loratadine did not provide sufficient exposure to SCH 34117. SCH 34117 induced a male-specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes at an oral dose of 12 mg/kg. An increase in pre-implantation and decreased number of implantations and fetuses were noted in female rats; reduced body weight and slow righting reflex were noted in pups. SCH 34117 was not teratogenic at oral doses up to 48 mg/kg.

No nonclinical studies have been performed for pseudoephedrine sulfate. There is, however, extensive clinical experience with this compound and it is approved for use in the indicated population in combination with loratadine, the parent compound of desloratadine.

General Toxicology Issues: The sponsor was previously informed that a 3-month toxicology study in one species and a teratology study in one species using the desloratadine/PSE combination would be needed for approval if desloratadine is not a marketed product. The original NDA for desloratadine (NDA 21-165) is currently considered to be Approvable. In addition, the sponsor agreed to perform a 2-year mouse carcinogenicity assay as a Phase 4 commitment.

Recommendations:

1. The NDA for Clarinex-D Extended Release Tablets for the treatment of seasonal allergic rhinitis and congestion is approvable from a preclinical perspective pending the approval of desloratadine in an alternate formulation or the submission of a bridging 3-month toxicology study and teratology study with the combination drug.

2. The sponsor should submit the final study report for the Phase 4 mouse carcinogenicity study within three years of the NDA 21-165 approval or study initiation, whichever occurs first. This comment was communicated to the sponsor following review of NDA 21-165.

Labeling with basis for findings: The review team decided to postpone review of the product label pending submission of updated label by the sponsor.

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ATTACHEMNT B.

Review of the Phase 4 Commitment

of 2-Year Carcinogenicity Study of Desloratadine in Mice

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-165**
SERIAL NUMBER:	**November 13, 2003**
DATE RECEIVED BY CENTER:	**November 14, 2003**
PRODUCT:	**Clarinex® (desloratadine) Oral tablets**
INTENDED CLINICAL POPULATION:	**Allergic Rhinitis**
SPONSOR:	**Schering-Plough**
DOCUMENTS REVIEWED:	**2-year carcinogenicity study of desloratadine in mice**
REVIEW DIVISION:	**Pulmonary and Allergy Drug Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy McGovern, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Anthony Zeccola**

Date of review submission to Division File System (DFS): January 25, 2005

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EXECUTIVE SUMMARY

II. Recommendations

D. Recommendation on approvability
Not applicable. The drug is approved and already on the market.

E. Recommendation for nonclinical studies
None.

F. Recommendations on labeling
Deferred. This review contains the finding of a 2-year carcinogenicity study of desloratadine in mice. The finding renders it necessary to update the labeling of all desloratadine products. The current application is only one of the desloratadine products on the market. The labeling revision of the current application is, therefore, deferred pending a labeling update to all applicable desloratadine products.

II. Summary of nonclinical findings

D. Brief overview of nonclinical findings

CD-1 mice (50/sex/dose) were treated orally with dietary desloratadine for 56-61 or 100 weeks to evaluate the carcinogenic potential of the drug. The respective desloratadine doses were 4, 16 and 48 mg/kg/day in the males and 10, 32 and 96 mg/kg/day in the females. The low- and mid-dose mice were treated for 101 weeks prior to sacrifice; the high dose group was treated for up to 61 weeks and the treatment was terminated. The surviving mice in the high dose were observed until their sacrifice at week 101. Plasma desloratadine levels increased proportionally to the dose. No significant increase in the tumor incidence was observed in any of the treatment groups. Desloratadine is considered non-carcinogenic in mice under the testing condition.

E. Pharmacologic activity
Not applicable to this review. See original NDA review.

F. Nonclinical safety issues relevant to clinical use
None.

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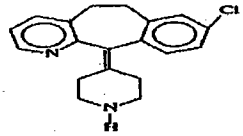
2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA Number: 21-165
Review Number :
Sequence number/date/submission type:
Information to the Sponsor: Yes ( ), No (X)
Sponsor/or Agent: Schering-Plough
Manufacturer of the Drug Substance: Schering-Plough

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Drug Products
HFD #: HFD-570
Review Completion Date: January 25, 2005

Drug:
Trade Name: Clarinex®
Generic Name: Desloratadine
Code Name: SCH 34117
Chemical Name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinyllidene)
CAS Register Number: N/A
Molecular Form and Weight: $C_{182}H3_{10}N_{40}N_{35}$
Structure:



Relevant IND/NDAs/DMFs: INDs 55364, 21,249, and 41,897
NDAs 19-658 (loratadine), 20-704, 21-300, 21-605.

Drug Class: Antihistamine

Intended clinical population: Allergic rhinitis in children 12 years of age and adults (5 mg once daily)

Clinical Formulation: (Per tablet) 5 mg desloratadine, corn starch, Talc, of carnauba wax and white wax

Route of Administration: Oral (tablets)

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Studies Submitted and Reviewed in the Review

24-Month Oral (diet) Carcinogenicity Study of SCH 34117 (Desloratadine) in Mice

Studies Submitted but Not Reviewed in this Review: None.

Background:

Desloratadine is a currently marketed H_1-histamine receptor antagonist indicated for allergic rhinitis. A 2-year carcinogenicity study of desloratadine in mice was conducted as a phase-4 commitment for Clarinex® in NDAs 21-165 and 21-300. The Senior Pharmacology and Toxicology Policy Group of the Center recommended the study in its evaluation of the carcinogenic potential of desloratadine on September 14, 1999. The Executive Carcinogenicity Assessment Committee of the Center reviewed the study protocol on August 1, 2000 under NDA 21-165.

The Policy Group recommendation was based on its review of the carcinogenicity studies of loratadine, the parent compound of desloratadine, in rats and mice. Loratadine is an Over-The-Counter drug with a trade name of Claritin®. Loratadine is transformed into desloratadine *in vivo*, although enzymes involved in the metabolism of both drugs have not been identified. Significant amounts of desloratadine are found in the blood after oral administration of loratadine. The loratadine studies apparently have evaluated the carcinogenic potential of both loratadine and, to a certain degree, desloratadine.

The loratadine carcinogenicity studies consist of an 18-month study in mice and a 2-year study in rats. In mice, males receiving 40 mg/kg/day of loratadine in the diet showed a significant increase in the incidence of hepatocellular tumors (adenoma and carcinomas). In rats, males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas). The plasma levels of desloratadine in mice receiving 40 mg/kg/day of loratadine were approximately 3 times that in humans. The plasma levels of desloratadine in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans.

The Policy Group concluded that the findings in rats were equivocal. The group also concluded that the nonclinical program of loratadine has adequately evaluated the carcinogenic potential of desloratadine in rats, but not in mice, based on the systemic exposure ratios of desloratadine between animals and humans. The primary deficiency of the mouse study was its lack of sufficient systemic exposure of desloratadine in mice. The group recommended conducting a 2-year carcinogenicity study of desloratadine in mice. The current study was completed in compliance with the recommendation of the policy group.

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2.6.2 PHARMACOLOGY

Not applicable because no information was submitted. Dr. Timothy McGovern reviewed the pharmacology of desloratadine in the application on September 29, 2000. Desloratadine (SCH 34117) is a selective H_1-receptor antagonist that is currently marketed in the US (approval date of 21-DEC-2001). Desloratadine inhibits the release of IL-4 and IL-13, and IL-6 and IL-8, histamine, tryptase, LTC_4 and PGD_2, and RANTES and attenuates eosinophil chemotaxis and adhesion. It also inhibits superoxide anion production by PMN, histamine-induced activation of endothelial cells, and P-selectin expression.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no information was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Dr. Timothy McGovern reviewed the pharmacokinetics and toxicokinetics of desloratadine in the application on September 29, 2000. Desloratadine is generally well absorbed after oral administration. Its oral bioavailability is 45-94% in rats and 47-57% in monkeys. Plasma concentrations of desloratadine increase supra-proportionally with dose in rats and monkeys. Tmax is achieved within 4 hours in rabbits, mice and monkeys and 1.5-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. In rats, desloratadine is widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Plasma protein binding of desloratadine is variable across species as the mouse, rat, monkey and humans demonstrates 94.4%, 90.5%, 85.8% and 85.0% binding, respectively.

Desloratadine is extensively metabolized in rats, mice and monkeys. The metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products (Figure 1, below). Metabolism of desloratadine occurs through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position is more extensive in humans. Male rats achieve relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. Excretion of desloratadine-related radioactivity is primarily through the feces with a large portion contributed through the bile. Approximately 20-40% is excreted through the urine.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable. See original NDA review.

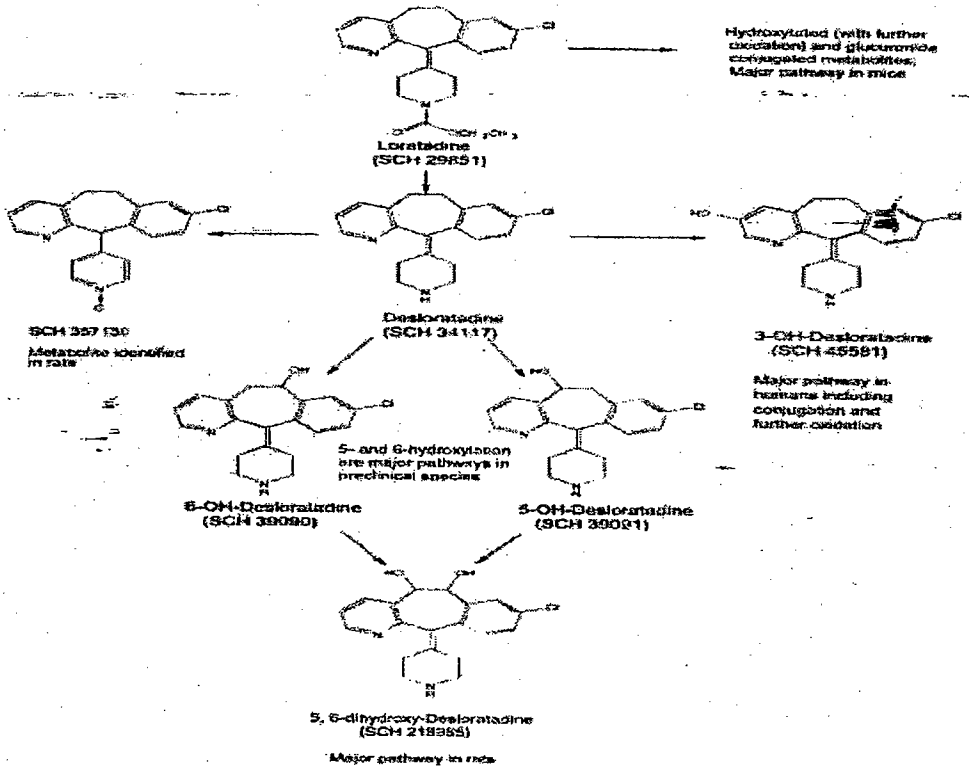

Figure 1. Metabolic pathways of loratadine and desloratadine.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Dr. Timothy McGovern reviewed toxicology of desloratadine in the current application in a review dated September 29, 2000. Desloratadine causes phospholipidosis in multiple organs in the laboratory animals. Toxicity of desloratadine has been evaluated in mice, rats and monkeys for up to 3-months duration. Studies of longer treatment duration are not available, neither are they required. The reason is that the available 3-month toxicity studies demonstrate that the toxicological profile of desloratadine is similar to that of another approved and currently marketed product, loratadine. The primary toxicity finding of desloratadine in these species, similar to loratadine, is systemic phospholipidosis in organ systems throughout the body. In mice, phospholipidosis occurs at 96 mg/kg/day and mortality occurs at 192 mg/kg/day after two months of treatment. In rats, treatment-related mortality occurs at a dose of 120 mg/kg in males and 30 mg/kg or greater in females in a three month study. Systemic phospholipidosis is the primary toxicity finding in tissues throughout the body. In addition, kidney necrosis and luminal cellular debris of the epididymides are also observed. The NOAEL in the 3-month toxicity study is 3 mg/kg in females and 30 mg/kg in males. These doses correlate to mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 1890 ng.hr/ml and 9490 ng.hr/ml in females and males, respectively. In monkeys, no treatment-related mortality

occurs at doses up to 18 mg/kg for 3 months. Phospholipidosis is again the primary toxicity finding in organs/tissues throughout the body. The NOAEL in the 3-month toxicity study is 12 mg/kg which results in mean systemic exposures ($AUC_{0\text{-}24\ hr}$) of 21,613 ng.hr/ml.

Carcinogenicity: Carcinogenicity of desloratadine is evaluated in 2-year traditional bioassays in mice and rats. Desloratadine is non-carcinogenic in mice and equivocal in rats. In mice, dDesloratadine at oral doses up to 32 mg/kg/day for 101 weeks did not cause significant increases in the incidence of any tumors in mice. Neither was there significant increase in any tumor incidence at 48 mg/kg/day for 56 weeks in the males and 96 mg/kg/day for 61 weeks in the females. The current review conducts a thorough review and evaluation of the study. The two latter doses exceeded the maximum tolerated dose because of the excessive mortality during the treatment period. The Executive CAC reviewed the study and considered desloratadine non-carcinogenic in mice.

In rats, males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas). The plasma levels of desloratadine in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans. The Senior Policy Group concluded that the findings in rats were equivocal.

The Mouse Study: Desloratadine is considered non-carcinogenic in mice under the testing condition.

CD-1 mice (50/sex/dose) were treated orally with dietary desloratadine for 56 or 100 weeks. The respective desloratadine doses were 4, 16 and 48 mg/kg/day in the males and 10, 32 and 96 mg/kg/day in the females. The low- and mid-dose mice were treated for 101 weeks prior to sacrifice; the high dose group was treated for up to 61 weeks and the treatment was terminated. The surviving mice in the high dose were observed until their sacrifice at week 101. Plasma desloratadine levels increased proportionally to the dose. No plasma AUC data, however, were available because of the paucity of data. A dose-related increase in mortality was observed. The respective survival rate for the control, low, mid and high dose groups at the end of study was 43%, 34%, 22% and 24% in the males and 58%, 46%, 46% and 24% in the females. The cause of death was apparently the disturbance on gastrointestinal motility associated with the anticholinergic side effect of the drug. There was no treatment-related decrease in body weight. The high dose males showed a statistically significant decrease in food consumption. The high dose group showed non-neoplastic changes that included focal necrosis of hepatocytes in the liver, lymphoid atrophy in the spleen. Dilated lumen of the large intestine was observed in the mid and high dose groups. No statistically significant increase in the incidence of any tumors was observed in any treatment groups.

This study has adequately tested the carcinogenic potential of desloratadine in mice. The study is designed and conducted per the Executive CAC recommendations. The species, dose selection, and duration of treatment are considered appropriate. Adequate number animals in the mid and low dose groups survived to the end of the study. The duration of treatment is adequate as the low and mid dose groups were dosed for at least 100 weeks. No statistically significant increase in the incidence of any tumors was observed in any treatment groups.

Desloratadine is considered non-carcinogenic in mice. The Executive CAC has concurred with the conclusion (See Exec. CAC minutes of November 16, 2004).

The Rat Study: The carcinogenicity potential of desloratadine rats was evaluated in a 2-year dietary loratadine study. Males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas). The plasma levels of desloratadine in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans. The Senior Policy Group of the Center reviewed the results on September 14, 1999. The group considered the finding equivocal. The group also concluded that the loratadine study in rats adequately evaluated the carcinogenic potential of desloratadine, based on the plasma levels of desloararadine between rats and humans.

2.6.6.2 Single-dose toxicity

Not applicable. See original NDA review.

2.6.6.3 Repeat-dose toxicity

Not applicable. See original NDA review.

2.6.6.4 Genetic toxicity

Not applicable because no information was submitted. Dr. Timothy McGovern reviewed the pharmacology of desloratadine in the application on September 29, 2000. Desloratadine tests negative in the following assays: the bacterial mutation in *S. typhimurium and E. coli* (Ames test), *in vitro* chromosome aberration assay using human lymphocytes, and *in vivo* mouse bone marrow erythrocyte micronucleus assay.

2.6.6.5 Carcinogenicity

The carcinogenic potential of desloratadine in mice and rats was evaluated to a certain extent previously in the loratadine development program. The loratadine carcinogenicity studies consist of an 18-month study in mice and a 2-year study in rats. In mice, males receiving 40 mg/kg/day of loratadine in diet showed a significant increase in the incidence of hepatocellular tumors (adenoma and carcinomas). In rats, males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas). The plasma level of desloratadine in mice receiving 40 mg/kg/day of loratadine were approximately 3 times that in humans. The plasma levels of desloratadine in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans.

The Senior Policy Group concluded that the findings in rats were equivocal. The group also concluded that a two-year carcinogenicity study of desloratadine in mice was needed based on the lack of adequate plasma desloratadine levels in the available study with loratadine. This additional study, however, could be completed as a phase 4 commitment. The sponsor has completed the study per the Executive CAC commendations regarding dose selection. This review evaluates the results of the study.

Study Title: 24-Month Oral (diet) Carcinogenicity Study of SCH 34117 (Desloratadine) in Mice

Key findings: The desloratadine treated groups did not show statistically significant increases in any tumors. Desloratadine is non-carcinogenic in mice under the test conditions.

STUDY IDENTIFICATION

Study No:	SN 97255
Date of Submission:	November 13, 2003
Volume #, and page #:	Volume 1, page 1
Conducting laboratory and location:	Safety Evaluation Center, Schering-Plough Research Institute, Lafayette, NJ 07848
Date of study initiation:	October 10, 2000
Date of Study Completion:	September 26, 2003
Study Report Date:	September 26, 2003
GLP compliance:	Yes, signed GLP statement included.
QA reports:	Yes, signed GLP statement included.
Drug lot #, & % purity:	Batch IRQ-99-19M1[2], Purity

STUDY PROTOCOL DESIGN AND METHODS

Study Type ():	Feed, 2-year bioassay
Species/strain:	Mouse
Number/sex/group; age at start of study:	50; 6 weeks of age
Animal weight at start of exposure:	Male: 23.5 – 33.9 g; female: 18.1 – 26.2 g.
Animal housing:	Individual caging, 20 ± 2°C; 12 hr light cycle;
Treatment Duration:	101 weeks for LD and MD; 56 – 61 weeks for HD
Feed and water:	fed *ad libitum*,);

[2] LOTs: AUG 17 00 2B, AUG 17 00 2B, SEP 01 00 1A, SEP 25 00 3A, OCT 03 00 3B, NOV 01 00 3A, NOV 01 00 3B, DEC 01 00 1A, DEC 07 00 3B, DEC 07 00 3C, JAN 01 01 2C, FEB 01 01 2A, FEB 01 01 2B, APR 01 01 1A, MAY 01 01 2B, MAY 03 01 3A, MAY 11 01 2A, JUN 11 01 2A, JUN 21 01 1A, JUL 01 01 3A, AUG 01 01 3A, AUG 01 01 3B, AUG 28 01 2C, SEP 01 01 3A, SEP 12 01 1A, OCT 01 01 1B, OCT 10 01 1C, NOV 01 01 3B, JAN 01 02 3C, FEB 01 02 1B, FEB 15 02 1A, FEB 15 02 1B, MAR 23 02 2A, APR 18 02 1A, MAY 15 02 1C, JUL 10 02 3B;

Formulation/vehicle: Desloratadine in [redacted] (meal). The test article was mixed in the diet at least every two weeks at estimated concentration to attain intended doses.

Drug stability/homogeneity: N/A

DESIGN

Design: Table 1 (next page) shows the overall design of the 24-month oral carcinogenicity study of desloratadine in mice.

Table 1. Design of the 24-Month Oral Carcinogenicity of Desloratadine in Mice

Group	Treatment	Desloratadine (mg/kg/day)		No. of Mice /sex		Treatment Duration (wks)
		Male	Female	Tox.	PK	
C1	Rodent diet	0	0	50	0	101
C2	Rodent diet	0	0	50	0	101
T1	Desloratadine	4	10	50	18	101
T2	Desloratadine	16	32	50	18	101
T3	Desloratadine	48	96	50	18	51 – 56 a

a. Survival mice were sacrificed at week 101.

DOSES:

Doses: Male: 4, 16 and 46 mg/kg/day; Female: 10, 32 and 96 mg/kg/day.[3]

Basis of dose selection: A 13-week oral study in mice (SN 97253, a QA report) shows that 48 and 96 mg/kg/day were the maximum tolerated dose (MTD) in males and females, respectively. The MTD was determined by reductions in body weight gain and phospholipidosis at higher doses. SN 97253 was reviewed by Dr. McGovern on 07-NOV-2000 in IND 55,364.

Relation to clinical use: This is a dietary study while clinical formulation is oral tablets and syrup indicated for allergic rhinitis.

CAC concurrence: Yes. The Executive CAC reviewed the study protocol on August 1, 2000 and recommended top doses of 48 and 96 mg/kg/day in male and females, respectively. Rationales for the recommendation can be found in Dr. McGovern's review dated 07-NOV-2000. The sponsor states that "the FDA (on August 30, 2002) recommended an early sacrifice of the high dose group when the animal number reached 12/sex." The sponsor further states that "[I]n consultation with the FDA, a decision was made to terminate dosing of the high-dose males in Week 56 and of the high-dose females in Week 61 when approximately 50% mortality was reached, respectively."

[3] Test article intake was calculated weekly during Weeks 1 through 24, every two weeks during Weeks 25 through 36 and every four weeks thereafter (all mice).

Restriction paradigm for dietary restriction studies: None.

Route of administration: Dietary. The percentage of drug in the diet was kept consistent throughout each dosing interval. (The variation was within 0.6% of the target dose.) The desloratadine concentration for a particular dosing period was derived from estimated food consumption and body weight of the period.

Frequency of drug administration: *ad libitum*

Controls employed: This study contains a dual control. The two control groups received identical treatment.

Interim sacrifices: No.

Satellite PK or special study group(s): 18 mice/treatment group for PK. Plasma samples were analyzed for both desloratadine and SCH 45581 (3-hydroxy desloratadine, a metabolite) using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay by [redacted].

Blood samples were centrifuged to separate the plasma. Equal volumes of plasma from each of the three mice were pooled for each time point, group and sex. When the plasma volume of an individual sample was considerably lower than the other two samples for the time point, group and sex, the low-volume sample was excluded from the pooling and discarded. Two hundred microliters of plasma each was used for the determination of desloratadine and SCH 45581.

Blood samples (target volume: 1.0 ml) were obtained from three satellite mice/sex/time point in each desloratadine dose group (0, 4, and 12 hours after the initiation of the 12-hour dark cycle) during Weeks 4 and 24 (via the abdominal aorta during isoflurane-induced anesthesia). Blood was collected into tubes containing heparin as the anticoagulant. The mice was bled in sequential numerical order and sacrificed by exsanguination during isoflurane-induced anesthesia after blood collection and cremated without necropsy.

Deviations from original study protocol:

Dosing in the high dose group was terminated prematurely because of excessive mortality associated with desloratadine toxicity. Desloratadine dosing was terminated at weeks 56 and 61 for the males and females, respectively. Surviving animals were observed until week 101 for scheduled sacrifice. The Agency agreed with the deviation on August 30, 2002.

OBSERVATIONS AND FREQUENCIES:

Viability:	Daily
Clinical signs:	Weekly
Body weights:	Weekly for weeks 4 – 24, every 2 weeks for weeks 25 – 36, and every week thereafter
Food consumption:	Weekly for weeks -1 – 24, every two weeks for weeks 25 - 36, and every 4 weeks thereafter
Ophthalmology:	Weeks -1, 53 and 99
Hematology:	Week 100 (MD) or 101/102 (C1, C2 and LD)

Clinical chemistry: None.

Gross pathology: Weeks 101 and 102 for C1, C2, LD and MD, week 56 for HD males and week 61 for HD females

Histopathology: Adrenal glands, aorta, thoracic, bone (femur and sternum) bone marrow (from for cytology, brain, epididymides, esophagus, eyes, gallbladder, Harderian Glands, head, heart, kidneys, large intestine – (cecum and colon), liver, lungs, lymph nodes (mandibular and mesenteric), mammary gland, ovaries, pancreas, parathyroid gland(s), peripheral nerve – sciatic pituitary gland, prostate gland, salivary glands (mandibular), seminal vesicles, skeletal muscle (biceps femoris), skin, small intestine (duodenum, jejunum, ileum), spinal cord, thoracolumbar, spleen, stomach, testes, thymus, thyroid gland, tongue trachea, urinary bladder, uterus (plus cervix), & vagina. All organs/tissues, gross findings and masses prepared for histopathologic examination were evaluated and a peer review was conducted.

Toxicokinetics: Weeks 4 and 24; 0, 4 and 12 hr after initiation of the 12 hr dark cycle on days 26 and 166

Palpable Mass Observations: Palpation for tissue masses was performed on toxicity portion mice once every four weeks during Weeks 4 through 24, every two weeks during Weeks 25 through 52, and weekly thereafter.

Statistical methods:

Data:	Statistical Method:
Body weight and food consumption:	None. Descriptive only.
Mortality:	Kaplan-Meier survival curve and log ranking test, $\alpha = 0.05$; controls combined
Tumor data:	Peto's linear trend test (alpha = 0.005 and 0.025 for common and rare tumors, respectively

RESULTS:

Mortality:

Significant mortality was observed in the MD and HD groups (Table 2). The mortality rate in the HD group was so high (approximately 55%) that the dosing of this group was terminated at weeks 56 (males) and 61 (females), respectively. The survival animals were observed without dosing until sacrifice at week 101. The mid dose groups had lower, but also significant, mortalities (20 and 15% for males and females, respectively). The cause of death was dilatation of the large intestine and impaction, distention and hardened content in the intestine related to anti-cholinergic effect of the drug.

Table 2. Number, Type and Cause of Deaths

Sex	Male					Female				
Desloratadine (mg/kg/day)	0	0	4	16	48	0	0	10	32	96
Unscheduled sacrifice	14	11	9	15	18	8	12	14	10	16
Found dead	12	16	24	24	20	11	14	13	17	22
Total	26	27	33	39	38	19	26	27	27	38
Intestine dilation	0/26	0/27	0/33	12/39	25/38	0/19	0/26	0/27	9/27	26/38
Incidental death	26	27	33	27	13	19	26	27	18	12
Terminal sacrifice	24	23	17	11	12	31	26	23	23	12
Survival rate (%)	40	46	34	22	24	62	52	46	46	24

No treatment-related mortality was observed in the satellite animals designated for pharmacokinetic studies. This is not unexpected because these animals were sacrificed prior to the occurrence of significant treatment-related mortalities in the main section of the study.

Figures 2 and 3 present the survival curve as a function of time. The HD group had an increased mortality rate starting approximately 6 months of the treatment.

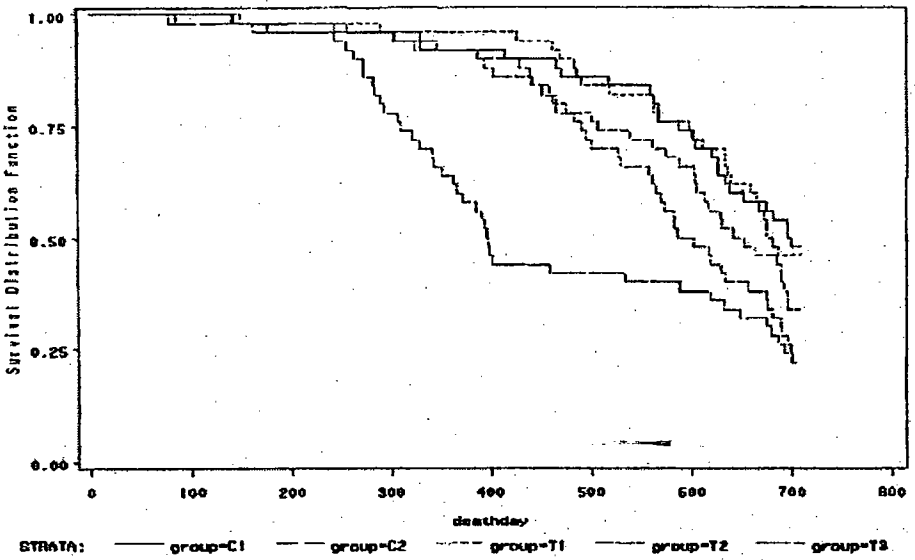

Figure 2. Kaplan-Meier survival curve of the 2-yr dietary carcinogenicity study of desloratadine in male mice. C1, C2, T1, T2 and T3 represents the Control 1, control 2, low dose, mid dose and high dose of desloratadine, respectively.

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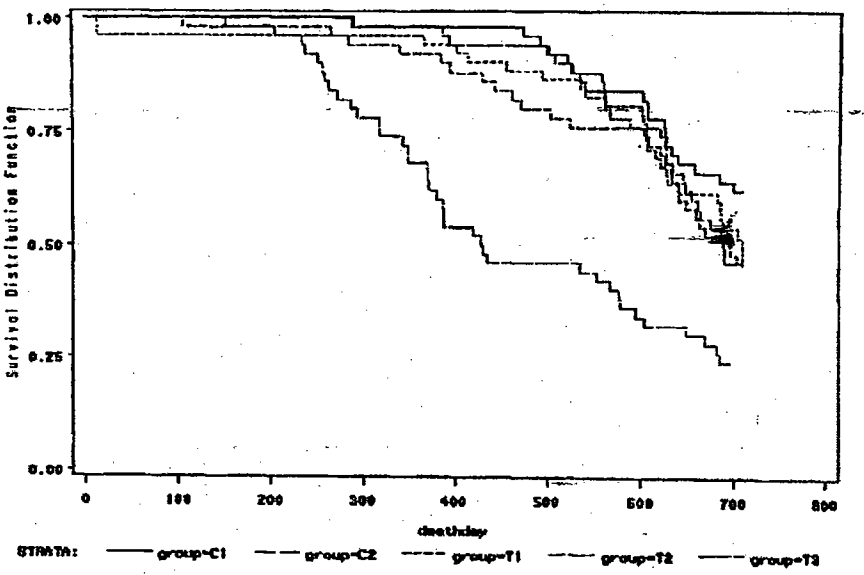

Figure 3. Kaplan-Meier survival curve of the 2-yr dietary carcinogenicity study of desloratadine in female mice. C1, C2, T1, T2 and T3 represents the Control 1, control 2, low dose, mid dose and high dose of desloratadine, respectively.

The desloratadine-induced deaths were attributed to the disturbance of gastrointestinal movement associated with its anticholinergic activity. The animals generally had clinical signs of distended abdomen, firm abdomen, abnormal stool (scant or non feces or enlarged stool), hypotonia of the anal sphincter, and/or dehydration. Necropsy findings included distended (with hard feces) or impacted colon and/or cecum, and dilatation of the large intestine.

Clinical signs: The MD and HD animals showed distended abdomen, firm abdomen, abnormal stool (scant or non feces or enlarged stool), hypotonia of the anal sphincter, and/or dehydration.

Palpable masses: No treatment-related effects were observed (Table 3).

Table 3. Palpable Masses

Sex	Male					Female				
Desloartadine (mg/kg/day)	0	0	4	16	48	0	0	10	32	96
Animal #	50	50	50	50	50	50	50	50	50	50
# Animal with masses	3	4	2	2	1	6	4	6	4	4
% Animal with masses	6	8	4	4	2	12	8	12	8	8
# Animal w/ multiple mass	0	0	0	0	0	1	2	1	0	1
Mean # masses/animal	0	0	0	0	0	0	0	0	0	0
Total number of masses	3	4	2	2	1	8	11	7	4	5
Mean onset (weeks)	74	59	84	63	32	63	76	71	80	82
# Deaths w/ masses	2	3	2	2	0	5	4	6	3	4
# Death w/ multi. masses	0	0	0	0	0	1	2	1	0	1

Body weight:

No significant effect was observed. Table 4 presents the differences in body weight of the treatment groups in comparison to the control groups at several major milestones of the study. These milestones are defined as Weeks 1, 26, 52, 78 and 100 of the treatment.

Table 4. Mean Body Weight

Sex	Male				Female			
Desloartadine	C1/C2 [a]	LD [b]	MD [b]	HD [b]	C1/C2 [a]	LD [b]	MD [b]	HD [b]
Week 1	27.8	1.8	0.7	-0.4	20.7	0.5	-1.9	0.5
N	100	50	50	50	100	50	50	50
Week 26	38.3	+2	+1	-4	28.7	+2	+3	+7
N	98	49	48	49	100	49	50	49
Week 52	39.6	+3	+1	-3	30.8	+4	4	3
N	94	46	46	32	99	46	49	34
Week 100	38.6	+3	+5	-2	31.9	+4	+2	+1
N	50	19	14	12	60	26	23	12

a. Actual body weight in grams (average of the Control 1 and Control 2 groups).
b. Difference from the control (%).

Figures 4 and 5 provide graphical presentations of body weight data as a function of treatment duration. Note that the treatment for the HD group (T3) stopped on week 56 and 61 for the males and females, respectively.

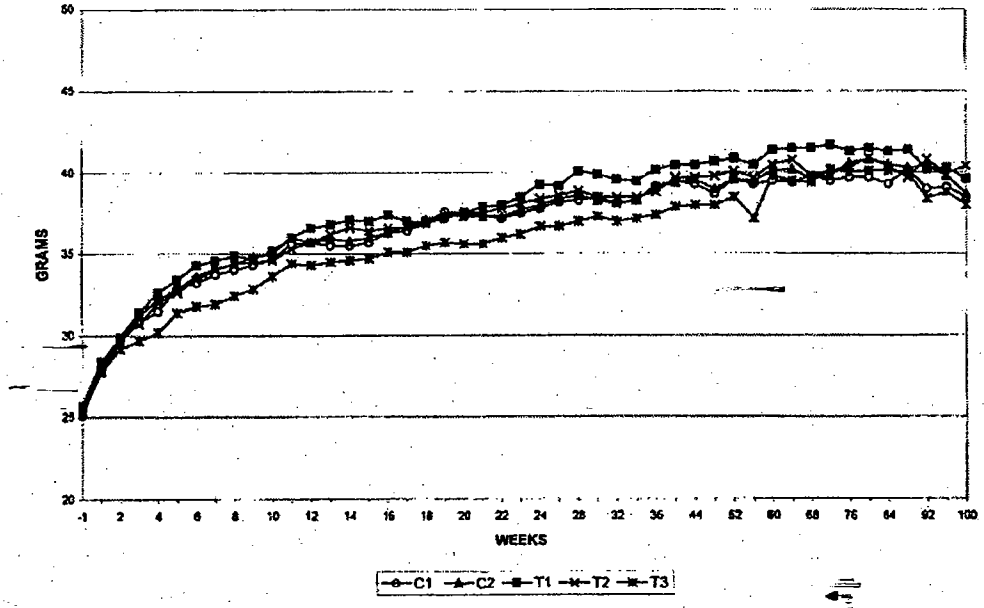

Figure 4. Body weight as a function of time male mice. C1, C2, T1, T2 and T3 represents the Control 1, control 2, low dose, mid dose and high dose of desloratadine, respectively.

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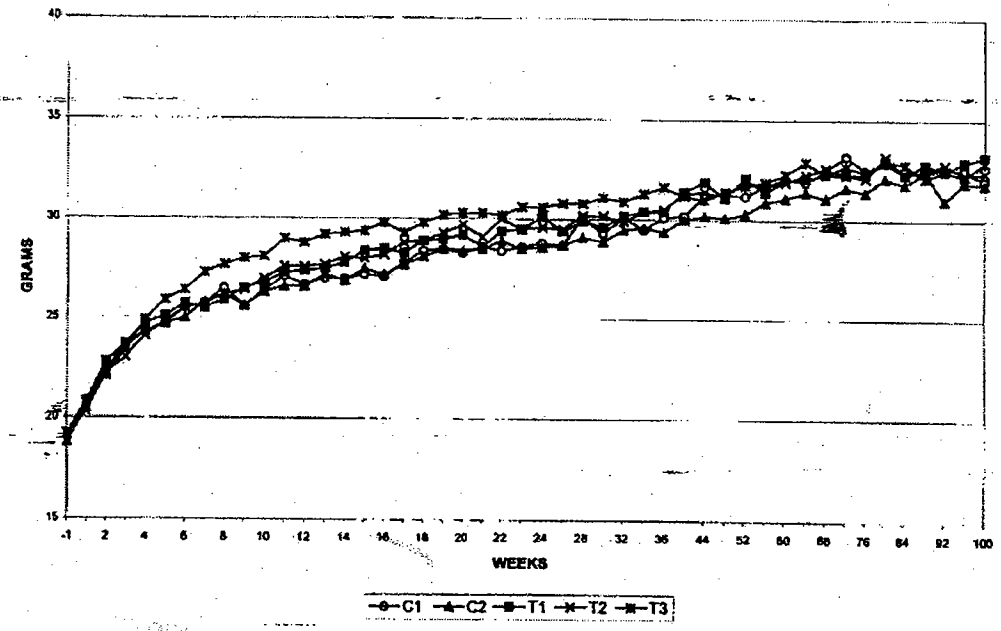

Figure 5. Body weight as a function of time female mice. C1, C2, T1, T2 and T3 represents the Control 1, control 2, low dose, mid dose and high dose of desloratadine, respectively.

Food consumption: The HD group showed decreases in food consumption in the treatment period (Figures 6 and 7). The respective decreases at weeks 26 and 52 were 8% and 4% in the males and 6% and 12% in the females. No significant difference in food consumption was observed upon the cessation of dosing.

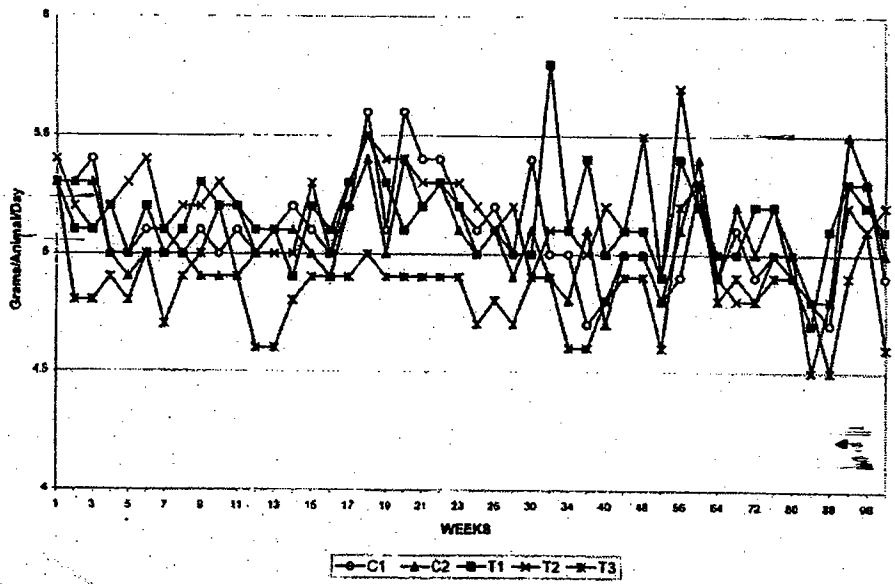

Figure 6. Food consumption in male mice C1, C2, T1, T2 and T3 represents the Control 1, control 2, low dose, mid dose and high dose of desloratadine, respectively.

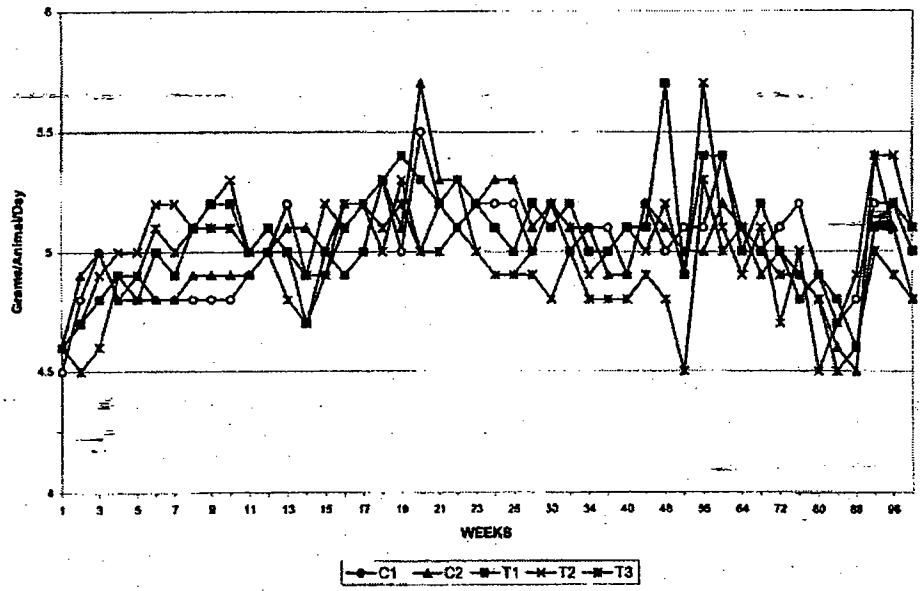

Figure 7. Food consumption in female mice. C1, C2, T1, T2 and T3 represents the Control 1, control 2, low dose, mid dose and high dose of desloratadine, respectively.

Ophthalmology: No treatment-related effects were observed.

Hematology: No remarkable changes were observed.

Gross pathology: The MD and HD groups showed impaction, distension, dilation and/or altered content (hard) of the large intestine. The respective total incidence of large intestine abnormality was 12 males and 9 females in the MD and 25 males and 26 females in the HD. The report attributes this finding to the anticholinergic effect of desloratadine.

Histopathology:

Non-neoplastic Changes:

Non-neoplastic changes associated with desloratadine treatment included dilated lumen of the large intestine, minimal focal necrosis of the hepatocytes, atrophy of lymphoid tissue in the spleen, and vacuolation of epithelial cells in the urinary bladder (Table 5, next page). Most findings are limited to the HD group. An exception was the intestine enlargement which also occurred in the MD group.

The liver lesion should be considered a treatment-related effect but it is not a major concern of the study due to its lack of associations with any neoplastic changes. The sponsor stated that the incidence of hepatic the lesion was "higher in the decedent males and females in the high-dose group and was primarily associated with the moribund condition of the animals" (the incidence in these animal was not given). The sponsor dismissed that finding because "hepatocellular necrosis is a commonly seen incidental finding in the liver of aging mice." Such a statement is not supported by the finding that the concurrent controls and lower dose

groups lacked significant liver lesion. Hepatocyte necrosis was not reported in the 3-month dose ranging study in mice. Neither are there studies of similar ages of mice for reference here.

Table 5. Histological Findings

Sex	Male					Female				
Desloratadine (mg/kg/day)	0	0	4	16	48	0	0	10	32	96
Animal #	50	50	50	50	49	50	50	50	50	50
Eye, retinal atrophy (total)	8	9/49	0/49	4/49	3	7/49	5/51	1/49	4/48	10
Minimal	7	4		3	3	5	4	1	4	4
Mild	1	4		1		1	1			3
Moderate		1				1				3
Large intestine, dilated lumen			1	13	26		3	3	11	27
Liver, focal necrosis (minimal)	2	1	8	5	11	9	8	5	8	14
Spleen, lymphoid atrophy	3	2	3	2	9	1	2	2	4	22
Minimal				1	2		1			5
Mild	1		3	1	7	1	1	2	1	8
Moderate		2							3	9
Urinary bladder, uroethelial vacuolation, minimal	1	1		2	7					4
Lumen dilation	12	18	13	23	23	1		2	4	4
Uterus, lymphoma (M), metastatic site						2	2	1	4	

A notable incidental finding was retinal atrophy (minimal to moderate). Although the incidence of retinal atrophy was comparable among treatment and control groups, the sponsor noted that "The severity of the retinal atrophy was slightly greater in the high-dose females (3) as compared to the concurrent controls (1)". The sponsor also indicated that "a comparable incidence and severity of retinal atrophy have been seen in the female control group of a previous carcinogenicity study in mice conducted at this facility". The sponsor concludes this finding incidental and the explanation seems reasonable. As noted above, this finding was not reported as part of the ophthalmologic exam.

Neoplastic Findings:

There was no significant increase in the incidences of any tumors in the desloratadine treatment groups, when compared to the concurrent controls. Dr. Ted Guo conducted a statistical analysis of tumor incidence (See Appendex 1, Dr. Guo's review dated August 13, 2004). Table 6 (next page) summarizes tumor incidences in the study.[4]

[4] The control group 2 in the females has a sample size of 52 in the Table 6 because it includes two mice (mice No. 598 and 600) that were replaced and sacrificed on day 12 of the study. These two mice were replaced due to "improper tattooing" (page 22 of the study report). They were examined microscopically. Ulcerations of the tattoo site were observed in both mice. No neoplastic lesions were observed in either mouse. The results were included in the study report. The review includes this number to be consistent with the study report. These two mice were excluded in the statistical analysis.

Table 6. Neoplastic Findings

Sex	Male					Female				
Desloartadine (mg/kg/day)	0	0	4	16	48	0	0	10	32	96
N	50	50	50	50	50	50	52	50	50	50
Adrenal glands										
Cortical cell adenoma						1				
Subcapsular cell adenoma		1				2				
Bone, osteosarcoma (M)[b]		1/49[a]						1/49		
Brain, meningioma	1					1				
Kidney, adenoma, renal tubule	2									
Liver, hepatocelullar adenoma	8	8	7	7	2/49		2	1		
Hepatocelullar carcinoma (M)	1	3	3	1		2				
Hemangiosarcoma	2			3	2					
Lungs, bronchoalveolar adeno.	10	15	5	4	3	7	9	5	3	4
Bronchoalveolar carcinoma-M	3	1	3	5	2	2		5	3	1
Squamous cell carcinoma (M)										1
Lymph N., hemangiosarcoma							1			
Mammary gland,										
Adenoacathoma (M)	0/5	0/5	0/3	0/5	0/18	2/46				
Adenocarcinoma (M)	0/5	0/5	0/3	0/5	0/18	1/46	2/49	2/46	1/47	3/48
Fibrosarcoma (M)	0/5	0/5	0/3	0/5	0/18				1/47	
Ovary, granulosa cell tumor										1
Luteoma							1/52			
Leiomyoma, mesovarian						1				
Pancreas, islet cell adenoma									1	1
Pituitary gland, adenoma						2/46	3/50	2/48	2/48	
Skin, Basal cell carcinoma (M)		1	1/49							
Basosquamous carcinoma (M)						1/49				
Fibrosarcoma (M)	1									
Spleen, hemangioma			1/49							
Hemangiosarcoma (M)		1/49	1/49				1/51	1		
Testes, hemangioma		1								
Interstitial cell adenoma	1	1	1	1		-	-	-	-	-
Urinary bladder, mesenchymal tumor									1	
Uterus, adenocarcinoma (M)						1				
Endometrial stromal polyp	-	-	-	-	-	3	4	1		
Hemangiosarcoma (M)	-	-	-	-	-			1	1	
Leiomyoma	-	-	-	-	-		1			
Primary site undetermined										
Granulocytic leukemia (M)		1	1			1				
Histiocytic sarcoma (M)	1					1	2	2	1	
Lymphoma (M)		2	2	5	2	7	6	9	7	2
Osteosarcoma (M)									1	
Schwannoma (M)				1						

a. The denominator indicates variations of N; b, malignant tumors and the specified indicates benign tumor. The absence of number indicates that the specific finding is not present.

There appears to be a dose-related increase in the incidence of malignant lymphoma in males when the high dose is excluded from the analysis. The review does not consider this observation a treatment-related effect, based on the background incidence of the tumor in the testing species. According to the ' tumor database cited by the sponsor, the mean background rate of malignant lymphoma (whole body or multiple organs) in male CD-1 mice is 4.1% and 9.1% in the males and females, respectively. . The database consists of 46 studies and 2565 mice in the males and 48 studies and 2822 mice in the females. In males, a total of 105 mice from 33 studies were reported to have malignant lymphomas. The incidence of the tumor among studies ranged from 1.43% to 21.67%. In females, a total of 274 mice from 41 studies were reported to have malignant lymphomas. The respective incidence of the tumor among studies ranged from 1.67% to 50.0%. The respective rate of malignant lymphoma in the current study ranges 0% - 10% in males and 12% - 18% in the females (incidence: 0-2/50, 2/50 and 5/50 for the control, low and mid dose in males and 6-7/50, 9/50 and 7/50 in the females). The rate of the malignant lymphoma of the treatment groups in the current study is well within the range of the background incidence. The slight increase in the tumor incidence in mid dose group should not be construed as a treatment-related effect.

Toxicokinetics:

Plasma desloratadine concentration rose in a dose-dependent fashion. SCH 45881 was not quantifiable in any of the samples. The detection limit was 0.1 and 0.025 ng/ml for desloratadine and SCH 45881, respectively. Table 7 summarizes the results of plasma desloratadine concentrations.[5] The females showed plasma desloratadine levels that were twice the levels in males but the females also received a two-fold higher dose than males. No AUC data were obtained due to the limited sampling times.

Table 7. Plasma Concentration of Desloratadine in a 24-Month Oral Carcinogenicity Study in Mice (N= 1)[a]

Treatment (week)	Time (hr)	Desloratadine (ng/ml)					
		Male			Female		
		4 mg/kg	16 mg/kg	48 mg/kg	10 mg/kg	32 mg/kg	96 mg/kg
4	0	78.3	325	1070	185	542	1910
	4	85.0	341	1080	227	611	1900
	12	83.3	496	1040	131	652	2300
24	0	57.2	357	1040	140	634	1820
	4	74.5	392	1100	171	660	2490
	12	73.5	405	1200	182	767	2190

a. The sample was 200 µl of plasma pooled from three mice per time point per dose.

[5] The Department of Drug Development and Pharmacokinetics, Schering-Plough Research institute, 2105 Galloping Hill Road, Kenilworth, NJ 07033, conducted the determination of the plasma drug concentrations (DESLORATADINE and SCH 45581) in . The analytic report was dated September 18, 2001 while the final toxicokinetic report was dated August 27, 2003.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The sponsor has completed a Phase 4 commitment to evaluate the carcinogenic potential of desloratadine in mice. Desloratadine is non-carcinogenic in mice. This study has adequately tested the carcinogenic potential of desloratadine in mice. The study is designed and conducted in a manner that is consistent with the ICH guidelines. Dose selection was per the Executive CAC recommendations. The species, dose selection, and duration of treatment are considered appropriate. Adequate number animals in the mid and low dose groups survived to the end of the study, although excessive mortality occurred in the high dose group (indicating that an MTD has been achieved). The duration of treatment is adequate as the low and mid dose groups were dosed for 100 weeks. No statistically significant increase in the incidence of any tumors was observed in any treatment groups. Desloratadine is considered non-carcinogenic in mice.

Conclusions:

The sponsor has adequately completed its Phase-4 commitment regarding the evaluation of the carcinogenic potential of desloratadine in mice. Desloratadine is not carcinogenic at oral doses up to 32 mg/kg/day for 2 years in mice. CD-1 mice (50/sex/dose) were treated orally with desloratadine in diet for 56 or 100 weeks. The respective desloratadine doses were 4, 16 and 48 mg/kg/day in the males and 10, 32 and 96 mg/kg/day in the females. The low- and mid-dose mice were treated for 100 weeks prior to sacrifice; the treatment in the high dose group was terminated at early as week 56 because of the excessive mortality. The surviving mice in the high dose were observed until their sacrifice at week 101. The mid dose males also showed a significant increase in mortality. The mortality was attributed to the disturbance on gastrointestinal motility associated with the anticholinergic side effect of the drug. The high dose group showed non-neoplastic changes that included focal necrosis of hepatocytes in the liver and lymphoid atrophy in the spleen. No statistically significant increase in the incidence of any tumors was observed in any treatment groups. The above results show that the maximum tolerated dose has been either achieved or exceeded. The study is adequately designed. The results do not show any evidence of carcinogenicity of desloratadine.

A previous study has demonstrated that desloratadine is equivocal in regard to its carcinogenic potential in rats. The current review finds that the drug is not carcinogenic in mice. The sponsor should update the labeling of desloratadine to include the finding of the mouse study.

Recommendations:

The sponsor should update the labeling of desloratadine to include the finding of the mouse study.

Luqi Pei, Ph.D.
Pharmacologist and Toxicologist

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APPENDIX/ATTACHMENTS

Minutes of the Executive CAC Meeting on August 1, 2000

Executive CAC
August 1, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Jeri El Hage, Ph.D., HFD-510, Alternate Member
C. Joseph Sun, Ph.D., HFD-570, Team Leader
Timothy McGovern, Ph.D., HFD-570, Presenting Reviewer

Author of Draft: Timothy McGovern, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA 21-165
Drug Name: SCH 34117, descarboethoxyloratadine
Sponsor: Schering Corporation

SCH 34117 is an active metabolite of the antihistamine loratadine indicated for the treatment of seasonal allergic rhinitis. The anticipated clinical dose is 5 mg/day. The compound was negative in the bacterial mutation assay, the chromosome aberration assay in cultured whole blood human lymphocytes, and the in vivo mouse micronucleus assay. The Senior Pharmacology/Toxicology Policy Group previously concluded that the rat carcinogenicity study of loratadine adequately assessed the carcinogenic potential of SCH 34117 and a waiver in this species was granted. The Group recommended that the sponsor perform a 2-year mouse carcinogenicity study as a Phase 4 commitment to fulfill its assessment of the carcinogenic potential of SCH 34117.

Mouse Dose Selection

The sponsor proposed doses of 8, 24 and 72 mg/kg/day administered in the diet for a 2-yr carcinogenicity study. The doses for the 24-month were selected based upon a determination of the MTD from a 3-month dietary administration study (doses of 24, 48, 96 and 192 mg/kg/day) and AUC ratio considerations derived from a 1-month toxicokinetic study performed using the doses assessed in the 3-month study. Evidence of significant enzyme induction from the 3-month study indicates that toxicokinetic data from the 1-month study may not accurately represent the systemic exposure to SCH 34117-related material in the 2-yr carcinogenicity assay. Thus, the MTD should be the sole parameter used for dose-selection. Drug-related mortality was observed at 192 mg/kg in males and body weight gain

was significantly reduced at doses of 96 mg/kg in males (27%) and 192 mg/kg in females (63%). Histological findings related to systemic phospholipidosis (vacuolation, atrophy) were observed throughout the body primarily at 96 and 192 mg/kg with tissue necrosis observed in numerous organs at 192 mg/kg. Kidney necrosis was also observed at a dose of 96 mg/kg in males. The doses of 48 and 96 mg/kg were considered the MTDs in males and females, respectively, due to reductions in body weight gain and findings associated with systemic phospholipidosis, especially necrosis, at higher doses.

Executive CAC Recommendations and Conclusions:

1. Doses of 4, 16, and 48 mg/kg in males and 10, 32 and 96 mg/kg in females are recommended based on a MTD endpoint.

2. The Committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately.

3. If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathological examination of other dose groups under any of the following circumstances:
   (a) For any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups.
   (b) For an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group.
   (c) For an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma, etc., see McConnell et al., JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level.
   (d) For an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

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Executive CAC
Date of Meeting: November 16, 2004

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
John Leighton, Ph.D., HFD-150, Alternate Member
Timothy McGovern, Ph.D., HFD-570, Team Leader
Luqi Pei, Ph.D., HFD-570, Presenting Reviewer

Author of Draft: Luqi Pei, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA No.: 21-165
Drug Name: Desloratadine
Sponsor: Schering Plough

Background:

Desloratadine is a currently marketed H_1-histamine receptor antagonist indicated for allergic rhinitis. This 2-year carcinogenicity study of desloratadine in mice was conducted as a phase-4 commitment for the approval of NDA 21-165 (Clarinex® tablets, approval date of December 21, 2001). The Senior Pharmacology and Toxicology Policy Group of the Center recommended the study in its evaluation of the carcinogenic potential of desloratadine on September 14, 1999. The Executive CAC concurred with the study protocol on August 1, 2000.

The Policy Group's recommendation was based on its review of the carcinogenicity studies of loratadine, a parent compound of desloratadine, in rats and mice. Loratadine is currently marketed as an Over-The-Counter drug (Claritin®). Since loratadine is transformed into desloratadine *in vivo*, a significant amount of desloratadine is found in the blood after oral administration of loratadine. The loratadine carcinogenicity studies, therefore, have evaluated the carcinogenic potential of both loratadine and, to a certain degree, desloratadine.

The loratadine carcinogenicity studies consist of an 18-month study in mice and a 2-year study in rats. In mice, males receiving 40 mg/kg/day of loratadine in diet showed a significant increase in the incidence of hepatocellular tumors (adenoma and carcinomas). In rats, males receiving 10 mg/kg/day of loratadine and both males and females receiving 25 mg/kg/day of loratadine showed significant increases in the incidence of hepatocellular tumors (adenoma and carcinomas).

Subsequent studies showed that the plasma level of desloratadine and related metabolites in mice receiving 40 mg/kg/day of loratadine were approximately 3 times that in humans. The plasma levels of desloratadine and related metabolites in rats receiving 25 mg/kg/day loratadine were approximately 30 times that in humans.

Based on the systemic exposure ratios of desloratadine and related metabolites between animals and humans, the Policy Group concluded that the nonclinical program of loratadine adequately evaluated the carcinogenic potential of desloratadine in rats, but not in mice. The primary deficiency of the mouse study was its lack of sufficient systemic exposure of desloratadine in mice. The group recommended conducting a 2-year carcinogenicity study of desloratadine in mice. The current study was completed in compliance with the recommendation of the Policy Group.

Mouse Carcinogenicity Study

CD-1 mice (50/sex/group) were treated with desloratadine in the diet for up to 101 weeks. Respective desloratadine doses were 4, 16 and 48 mg/kg/day in the males and 10, 32 and 96 mg/kg/day in the females. The study also included dual dietary controls. Due to excessive mortality, the treatment for the high dose mice was discontinued at weeks 56 and 61 for the males and females, respectively. The cause of death was the disturbance of the gastrointestinal motility associated with the anticholinergic property of the drug. Survivors of the HD group were observed for the remaining time of the study and were sacrificed at week 101 along with the other groups. A microscopic examination of a complete panel of tissues and organs was done for all animals. There was no evidence of treatment-related increases in any tumors.

The Executive CAC concurred with the dose selection and the study protocol on August 1, 2000. The Agency also concurred with the discontinuation of treatment for the high dose group in both sexes.

Executive CAC Recommendations and Conclusions:

* The Committee concurred that the study was valid.

* The Committee concurred that there were no drug-related tumor findings in the study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

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/TMcGovern, HFD-570
/LPei, HFD-570
/TZeccola, HFD-570
/ASeifried, HFD-024

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ATTACHMENT C.

Sponsor's Calculation of Exposure Ratios of Desloratadine between Mice and Humans (Submission of February 10, 2005).

Steady-state toxicokinetic parameter estimates for desloratadine were obtained following oral administration (via dietary admixture) of desloratadine to mice for 28 days (**SN 00133**). Systemic exposure to desloratadine was independent of the sex of the mouse and increased dose-proportionally over the dose range of 8 to 72 mg/kg. The largest desloratadine doses in the oncogenicity study in the mouse were 16 mg/kg and 32 mg/kg for males and females, respectively (**SN 97255**). Since the TK study doses did not correspond to the doses in the oncogenicity study, exposure estimates were obtained from the linear regression (weighted 1/dose^2) of exposure versus dose for the TK study (**Figure 1**).

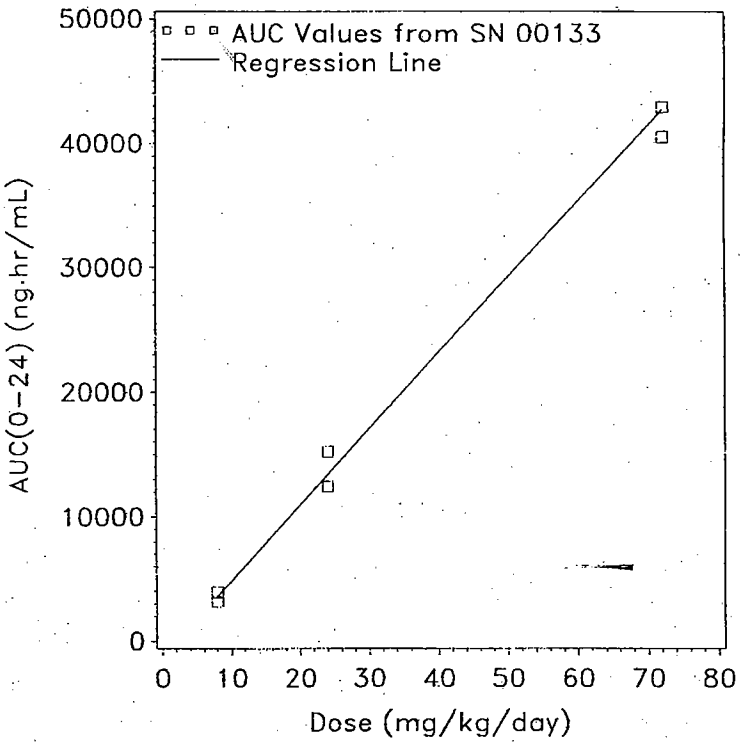

Figure 1 Least-squares linear regression of the mouse steady state AUC(0-24 hr) values versus dose.

The predicted exposures for desloratadine were 8481 and 18258 ng·hr/mL for doses of 16 mg/kg (male) and 32 mg/kg (female). Using the desloratadine exposure in humans after administration of a 5 mg tablet (56.9 ng·hr/mL, **P00275**), exposure multiples for desloratadine would be 149 (male) and 321 (female).

Since desloratadine is extensively metabolized in mice, rats and humans (normal metabolizers), exposure multiples in the NDA (21-165) for the 5 mg desloratadine tablet were

based on a comparison of maximal potential exposure to desloratadine and its metabolites. An exposure ratio of total radiocarbon (desloratadine equivalents)/desloratadine was obtained from the single dose ^{14}C-studies in mice, rats, and humans (**SN 97308, SN 97307, C98-097**). The exposure to total radiocarbon was 2.7-fold, 4.5-fold and 12.5-fold greater than parent drug for mice, rat, and humans, respectively. Then, the AUC values for desloratadine obtained in mice and rats administered with loratadine (**D-25201, D-25200**) and in humans administered 5 mg desloratadine (**P00275**) were multiplied by the exposure ratio to obtain exposure to desloratadine and its metabolites. Finally, the animal-to-human multiples were calculated for "unbound radiocarbon" using the protein binding data for desloratadine in each species (mouse 94.7% bound, rat 87.5% bound, human 86.2% bound, **SN 99215**).

Thus using the approach presented in the NDA and the predicted desloratadine exposures for the mouse oncogenicity study (**SN 97255**), the mouse-to-human exposure multiples for "unbound radiocarbon," representing both desloratadine and it metabolites, were estimated as 12 (male) and 27 (female) for doses of 16 mg//kg and 32 mg/kg, respectively.

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/s/

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I concur.