

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-313**

**PHARMACOLOGY REVIEW(S)**

## INTEROFFICE MEMO

TO: NDA 21-313, CLARINEX-D 12 HOUR (Schering Corporation)  
FROM: Timothy J. McGovern, Ph.D., Supervisory Pharmacologist  
DATE: January 31, 2006

This drug product is a combination of desloratadine (antihistamine) and pseudoephedrine (decongestant) indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion. This application was originally considered to be approvable from the nonclinical perspective as per the original nonclinical review of October 26, 2001 and the Agency letter of October 26, 2001. From a nonclinical perspective, the sponsor adequately addressed the relevant toxicologic issues including chronic toxicity, reproductive toxicity, genetic toxicity and carcinogenicity and the application was recommended for approval pending the approval of desloratadine in an alternate formulation or the submission of a 3-month bridging toxicology study and a teratology study with the combination of desloratadine and pseudoephedrine. Further, it was noted that a 2-year carcinogenicity study in mice with desloratadine should be completed as a Phase 4 commitment to further evaluate the carcinogenic potential of desloratadine within 3 years of approval of NDA 21-165 (CLARINEX tablets).

Dr. Luqi Pei conducted the primary review of the sponsor's resubmission and concluded that the outstanding issues have been addressed. Namely, the carcinogenicity study with desloratadine in mice was conducted and the study was reviewed and evaluated by the Executive CAC under NDA 21-165. The study was considered to be valid and the relevant information has been included in all of the CLARINEX product labels. Additionally, it was concluded that a 3-month toxicology and an embryo-fetal development study were not necessary since numerous desloratadine formulations have been approved. Therefore, Dr. Pei concluded that the application is approvable from a nonclinical perspective. Dr. Pei recommended a few edits to the product label in response to the sponsor's proposed modifications. The sponsor agreed with all of the recommendations.

In conclusion, the application is recommended for approval from a nonclinical perspective.

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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: 21-313  
SERIAL NUMBER: 000, Resubmission, AZ  
DATE RECEIVED BY CENTER: July 29, 2005  
PRODUCT: Clarinex<sup>®</sup>-D 12 Tablets  
INTENDED CLINICAL POPULATION: Allergic Rhinitis  
SPONSOR: Schering Corporation  
DOCUMENTS REVIEWED: Complete response to the 26-OCT-01  
AE letter  
REVIEW DIVISION: Pulmonary and Allergy 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 12, 2006

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## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

#### **A. Recommendation on approvability**

Approval is recommended from nonclinical perspective.

#### **B. Recommendation for nonclinical studies**

None.

#### **C. Recommendations on labeling**

Minor revisions to the proposed labeling are recommended. Clarinex<sup>®</sup> D24 Extended-Release tablets (NDA 21-605, approved on March 3, 2005) and Clarinex<sup>®</sup> D12 tablets (NDA 21-313) not only contain the same active ingredients (i.e., desloratadine and pseudoephedrine) but also administer the same total daily dose for each active ingredient. The proposed labeling for Clarinex<sup>®</sup> D12 tablets is generally consistent with that of the approved product labeling for Clarinex D24 Extended-Release tablets. No additional relevant nonclinical data on either active ingredient have become available since then. The submission, however, did contain a few minor and unnecessary revisions from the approved labeling for Clarinex D24 tablets. The review concludes that Clarinex<sup>®</sup> D12 and D24 tablets use the same labeling. The review thus rejects those newly proposed revisions, with the exception of the revision to the Pregnancy Category C section. See the Labeling Review section for detailed recommendations.

### **II. Summary of nonclinical findings**

#### **A. Brief overview of nonclinical findings**

See original NDA review of October 23, 2001.

#### **B. Pharmacologic activity**

See original NDA review of October 23, 2001. See original NDA review of October 31, 2001.

#### **C. Nonclinical safety issues relevant to clinical use**

None.

## 2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

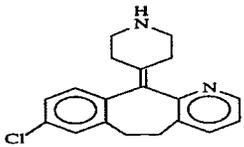
### 2.6.1 INTRODUCTION AND DRUG HISTORY

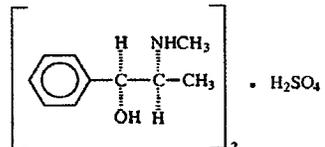
**NDA Number:** 21-313  
**Review Number :** 2  
**Sequence number/date/submission type:** 000/ 29-JUL-05/ AZ  
**Information to the Sponsor:** Yes ( ), No ( x )  
**Sponsor/or Agent:** Schering Corporation  
**Manufacturer of the Drug Substance:** Schering Corporation

**Reviewer Name:** Luqi Pei, Ph.D.  
**Division Name:** Pulmonary and Allergy Drug Products  
**Review Completion Date:** January 10, 2006

**Drug:**  
**Trade Name:** Clarinex<sup>®</sup>-D 12 Tablets  
**Generic Name:** Desloratadine and Pseudoephedrine  
**Code Name:** SCH 483 (combination product); SCH 34117 or DCL for desloratadine and PSE for pseudoephedrine  
**Chemical Name:** Desloratadine: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene),  
 Pseudoephedrine (PSE): -[1-(methylamino) ethyl]-[S-(R\*,R\*)]-benzenemethanol sulfate (2:1) (salt)

**CAS Register Number:** N/A  
**Molecular Form and Weight:** Desloratadine: C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>/310.8  
 Pseudoephedrine: (C<sub>10</sub>H<sub>15</sub>NO)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>

**Structure:**  
 Desloratadine:
 

Pseudoephedrine:
 

**Relevant IND/NDAs/DMFs:** INDs 55,364, 21,249, 41,897 and 58,506  
 NDAs 21-165, 21-297, 21-300, 21-312, 21-313, 21-363 & 21-563, 21-605 and 19-658 (loratadine)

**Drug Class:** Antihistamine and decongestant

**Intended clinical population:** Allergic rhinitis in children 12 years of age and adults twice daily

**Clinical Formulation:** Each tablet contains 2.5 mg desloratadine and 120 mg

pseudoephedrine. See Dr. McGovern's review dated October 31, 2001 for other ingredients.

**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:**

The original application for Clarinex<sup>®</sup> D12 (NDA 21-313) was filed on December 11, 2000. The active ingredients of Clarinex<sup>®</sup> D12 tablets are desloratadine (2.5 mg) and pseudoephedrine (120 mg). The Division issued an approvable letter on October 26, 2001. The sponsor submitted a complete response to the Approvable letter on July 29, 2005.

Dr. Timothy McGovern conducted the pharmacology and toxicology reviews of NDA 21-313 on October 23, 2001. The review identifies the nonclinical deficiencies of the application. Specifically, a few toxicity studies of desloratadine and pseudoephedrine in combination are recommended prior to the approval since desloratadine had not yet been approved.

Since the issuance of the AE letter, a number of desloratadine products have been approved. One of the products, Clarinex<sup>®</sup> D24 (NDA 21-605, approved on March 3, 2005), is similar to the current application. The only difference between Clarinex<sup>®</sup> D24 extended-release tablets and Clarinex<sup>®</sup> D12 tablets is that the former contains twice as much of the active ingredients as the latter. Nonetheless, the total daily dose of each active ingredient in Clarinex<sup>®</sup> D12 and Clarinex<sup>®</sup> D12 is identical. This will be achieved by adjusting the frequency of administration. The recommended use for Clarinex<sup>®</sup> D24 is once a day and twice a day for Clarinex<sup>®</sup> D12. The approval and marketing of the desloratadine products render the nonclinical deficiencies identified in Dr. McGovern's review no longer outstanding. The current review clarifies these issues.

#### **2.6.2 PHARMACOLOGY**

Not applicable because no new data were submitted.

#### **2.6.3 PHARMACOLOGY TABULATED SUMMARY**

Not applicable because no new data were submitted.

**2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

Not applicable because no new data were submitted.

**2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

Not applicable because no new data were submitted.

**2.6.6 TOXICOLOGY**

Not applicable because no new data were submitted.

**2.6.7 TOXICOLOGY TABULATED SUMMARY**

Not applicable because no new data were submitted.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS****Conclusions:**

The nonclinical discipline recommends the approval of the Clarinex<sup>®</sup> D12 tablet application. The active ingredients of Clarinex<sup>®</sup> D12 tablets are desloratadine (2.5 mg) and pseudoephedrine (120 mg). Dr. Timothy McGovern conducted the pharmacology and toxicology review of the application on October 23, 2001. The review identified some nonclinical deficiencies. These deficiencies are, however, no longer considered outstanding as discussed in the review. The approval for the Clarinex D-12 tablet application is, therefore, recommended from the nonclinical discipline.

Dr. McGovern's review recommended two toxicity studies as the prerequisite for the approval of the Clarinex<sup>®</sup> D12 tablet application. These studies were a 3-month bridging general toxicity study in one species and a teratology study in one species with the desloratadine and pseudoephedrine combination. The review stated that the prerequisite was applicable only if the approval of Clarinex<sup>®</sup> D12 application occurred prior to the approval of any desloratadine-only products. (No desloratadine product was approved then.) The review also recommended a 2-year carcinogenicity study in mice as a Phase-4 commitment to NDA 21-165 (5 mg desloratadine tablets) which was the first application of desloratadine-only product applicable filed with the Agency.

A number of desloratadine only products have been approved since then. These products include desloratadine tablets (NDAs 21-165, 21-297 and 21-363), Reditabs (NDA 21-312), syrup (NDAs 21-300 and 21-563). Clarinex<sup>®</sup> D24 extended-release tablets, that contain both

desloratadine and pseudoephedrine, were also approved (NDA 21-605, approved on March 3, 2005). The only difference between Clarinex<sup>®</sup> D24 extended-release tablets and the Clarinex<sup>®</sup> D12 tablets is that the former contain twice as much the active ingredients as the latter. Through adjustment in the frequency of administration, the total daily dose of each active ingredient in Clarinex<sup>®</sup> D12 and Clarinex<sup>®</sup> D12 is identical. The recommended use is once a day for Clarinex<sup>®</sup> D24 and twice a day for Clarinex<sup>®</sup> D12, respectively.

The approval and marketing of the desloratadine products, including Clarinex<sup>®</sup> D24 extended-release tablets render the nonclinical bridging toxicity studies recommended by Dr. McGovern in his review dated October 23, 2001, unnecessary. The phase-4 commitment of the 2-year carcinogenicity study of desloratadine in mice has been completed and reviewed (Ref. pharmacology and toxicology review by Dr. Luqi Pei dated January 25, 2005 in NDA 21-165). Thus, the application no longer has any outstanding nonclinical issues. The approval of the Clarinex<sup>®</sup> D12 tablets application is recommended from the nonclinical discipline.

**Unresolved toxicology issues:** None

**Recommendations:**

This application is recommended for approval from a nonclinical perspective.

**LABELING REVIEW:**

Minor revisions to the proposed labeling are recommended. The Agency recently approved the labeling for the Clarinex<sup>®</sup> D24 extended release tablets (ref. NDA 21-605, approval date 03-MAR-2005). The nonclinical section of the labeling was based on Dr. Luqi Pei's review dated February 16, 2005 in the Clarinex<sup>®</sup> tablets application (NDA 21-165). The total daily doses of desloratadine and pseudoephedrine, the active ingredients for both Clarinex<sup>®</sup> D24 and Clarinex<sup>®</sup> D12 tablets, are identical. No additional relevant nonclinical data on either active ingredient have become available since then. The nonclinical labeling for the Clarinex D12 should, therefore, be compliant with that of the Clarinex D24.

The proposed product label for the relevant nonclinical sections for NDA 21-313 is generally acceptable because it is consistent with that in the approved product label for Clarinex D24. The lack any novel data renders a detailed review to the proposed product label unnecessary. The submission, however, did contain a few minor and unnecessary revisions from the approved labeling for Clarinex D24 tablets. As indicated earlier, the nonclinical section of Clarinex D24 tablets was based on data collected on desloratadine applications. There are currently multiple desloratadine products on the market: Clarinex tablets (NDAs 21-165, 21-297 and 21-363), Reditabs (NDA 21-312), syrup (NDAs 21-300 and 21-563). These products, including Clarinex<sup>®</sup> D24, carry a common labeling regarding the nonclinical data. As another derivative product of desloratadine, Clarinex<sup>®</sup> D24 tablets should also comply with the approved labeling. Although some of the proposed revisions might improve the

labeling slightly, such improvement is not significant enough to warrant an update of labeling for all desloratadine products. Thus, these proposed revisions, with the exception of the revision to the Pregnancy Category C section, should not be approved. The labeling for Clarinex D24 and D12 tablets, with the exception of the revision to the Pregnancy Category C section, should be identical.

The review will not list the full labeling. It lists the sections that need revisions instead. The recommended insertions and deletion to the sponsor's proposal are indicated by underlines and strikeouts, respectively.

Lines 41 – 43: (Clinical Pharmacology section):

... Results of a radiolabeled tissue distribution study in rats and a radioligand H1-receptor binding study in guinea pigs showed ~~\_\_\_\_\_~~ that desloratadine does not readily cross the blood brain barrier.

Lines 231-232 (Effect on QTc section):

[New paragraph] Single dose ~~\_\_\_\_\_~~ administration of desloratadine did not alter the corrected QT interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, intravenous).

Lines 334 – 336 (Carcinogenesis... section):

The estimated desloratadine and ~~\_\_\_\_\_~~ metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

Lines 370 – 372 (Pregnancy Category C section): The proposal is acceptable. The Sponsor proposed to use "CLARINEX-D<sup>®</sup> 12 HOUR Extended Release Tablets" ~~\_\_\_\_\_~~ ~~\_\_\_\_\_~~ in the lines 370-372. The text now read as:

... Because animal reproduction studies are not always predictive of human response, CLARINEX-D<sup>®</sup> 12 HOUR Extended Release Tablets should be used during pregnancy only if clearly needed.

The revision is acceptable since it is consistent with the CFR requirements.

Luqi Pei, Ph.D.

Pharmacologist and Toxicologist

**APPENDIX/ATTACHMENTS**

Not applicable.

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this page is the manifestation of the electronic signature.**  
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/s/  
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Luqi Pei  
1/12/2006 01:02:32 PM  
PHARMACOLOGIST

Timothy McGovern  
1/12/2006 03:19:03 PM  
PHARMACOLOGIST  
I concur.

## 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-piperidinylidene)

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

CAS registry number: NA

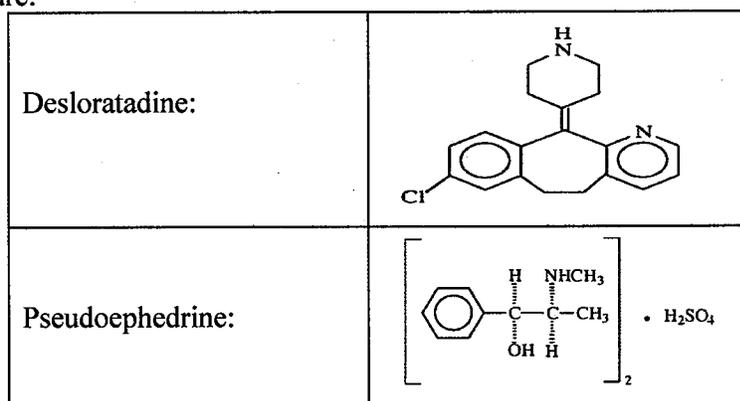
Mole file number: NA

Molecular formula/molecular weight:

DCL:  $C_{19}H_{19}ClN_2/310.8$

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

**Structure:**



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                   | 2.5       | PSE USP               | 120       |

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<sup>2</sup> desloratadine and 4.8 mg/kg or 177.6 mg/m<sup>2</sup> 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 ~~\_\_\_\_\_~~

~~\_\_\_\_\_~~ Submission 000 B2, Volume 4.6.

Study 00135: Mouse bone marrow erythrocyte micronucleus study of SCH 34117 with

~~\_\_\_\_\_~~, 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<sub>1</sub>-receptors over H<sub>2</sub> or H<sub>3</sub>-receptors. This finding was confirmed in isolated guinea pig lung tissue. SCH 34117 also demonstrated H<sub>1</sub>-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 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.

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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## 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<sub>1</sub>-receptors over H<sub>2</sub> or H<sub>3</sub>-receptors and displayed a 14-fold greater affinity for the H<sub>1</sub>-receptor than loratadine in cloned H<sub>1</sub> human receptor subtypes (IC<sub>50</sub> = 51 and 721 nM, respectively). This finding was confirmed in isolated guinea pig lung tissue (IC<sub>50</sub> = 840 and 3030 nM for SCH 34117 and loratadine, respectively). SCH 34117 was also ~ 18-fold more potent than loratadine in rat brain H<sub>1</sub>-receptor activity (SCH 34117 K<sub>i</sub> = 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<sub>50</sub> = 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<sub>1</sub> and M<sub>3</sub> receptor subtypes (IC<sub>50</sub> = 48 and 125 nM). In a separate study, SCH 34117 showed greatest activity at central H<sub>1</sub> receptors (IC<sub>50</sub> = 17 nM) while activity at peripheral H<sub>1</sub> receptors was similar to that at M<sub>2</sub> muscarinic receptors (IC<sub>50</sub> = 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<sup>1</sup>, loratadine (30 and 100 mg/kg, IV) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61

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<sup>1</sup> 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 H<sub>1</sub> antagonists: comparative studies with loratadine, terfenadine and sedating antihistamines in guinea-pigs. *Clinical and Experimental Allergy*, 25: 974-984.

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-

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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  $\mu$ M. 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  $\mu$ M) also inhibited a cloned human hKv1.5 current with an  $K_D$  of 12.5  $\mu$ M, but was less potent than loratadine or terfenadine ( $K_D=1.0$  and 0.8  $\mu$ M, 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  $\mu$ M) failed to significantly alter HERG currents. Both drugs (up to 10  $\mu$ M) had minimal effects on  $I_{HERG}$  current (15-20%) compared to terfenadine and quinidine ( $IC_{50} = 82$  and 168 nM, respectively). SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10  $\mu$ M) 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  $\mu$ M. SCH 34117 also decreased  $V_{max}$  and velocity of impulse conduction and increased excitation threshold ( $\geq 30$   $\mu$ M) while producing a negative inotropic effect (10  $\mu$ M) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100  $\mu$ M. In isolated rabbit ventricular myocytes, SCH 34117 (100  $\mu$ M) reduced  $Na^+$  current more effectively than 100  $\mu$ M loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) current to ~ 1/2 control value at  $6 \times 10^{-6}$  M as the concentration at which 1/2 current is blocked ( $k_{0.5}$ ) was  $5 \times 10^{-6}$  M ( $k_{0.5}$  for loratadine was  $8.7 \times 10^{-6}$ ). SCH 34117 had no effect at  $10^{-5}$  M on inward rectifier current (iK1) although the curve was flatter at  $3 \times 10^{-5}$  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.

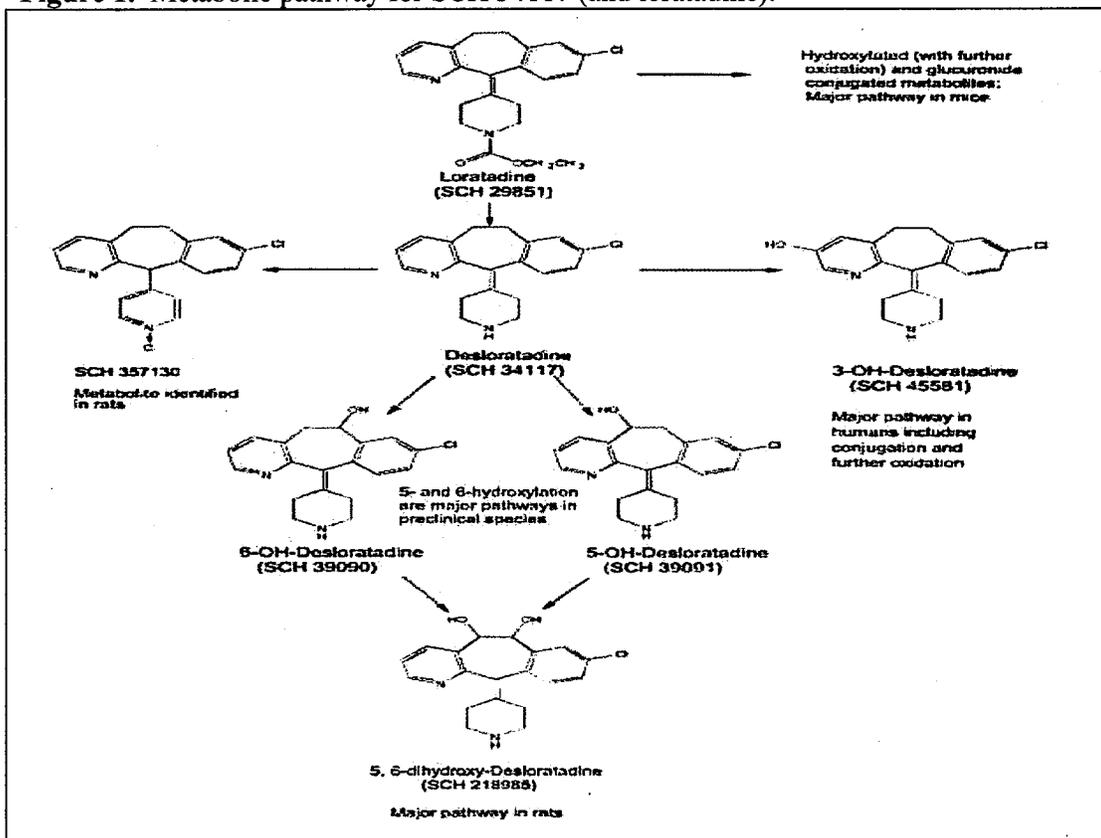
**Safety pharmacology conclusions:** Appropriate safety pharmacology studies were performed with SCH 34117 and no significant concerns were observed. SCH 34117 has been shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac  $K^+$  channels as well as a cloned 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. T<sub>max</sub> 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 <sup>14</sup>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 \_\_\_\_\_ and \_\_\_\_\_ were detected in male rat plasma 3 hours following oral administration of 6.5 mg <sup>14</sup>C-SCH 34117/kg. None was detected in urine samples. *In vitro* incubations of <sup>14</sup>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 \_\_\_\_\_; \_\_\_\_\_ 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

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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:** 0.4% aqueous methylcellulose

**Methods (unique aspects):** Animals were dosed by oral gavage on a daily basis for 91 or 92 days

**Dosing:**

Species/strain: Rat ~~\_\_\_\_\_~~

#/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

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|                     |  |
|---------------------|--|
| 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; all 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, chromorrhinorrhea, 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<br>F: ↑6 | M: ↓23<br>F: no Δ | M: ↓30<br>F: ↓4 | M: ↓30<br>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, 29, 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 vacuolation, 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 | 10 |
| Vacuolation, myofiber<br>minimal             | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 2  | 1  |
| Eyes   | 10 | 1  | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mineralization, corneal<br>minimal           | 0  | 0  | 0  | 3  | 0  | 0  | 0  | 0  | 0  |
| Heart  | 10 | 1  | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Degeneration, myofiber, focal<br>Minimal     | 0  | 0  | 0  | 2  | 1  | 1  | 0  | 0  | 0  |
| Kidneys                                      | 10 | 1  | 1  | 10 | 10 | 10 | 1  | 10 | 10 |
| Single cell necrosis, tubular<br>Minimal     | 0  | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  |
| Cell infiltration, mononuc cell<br>Minimal   | 0  | 1  | 0  | 1  | 0  | 1  | 0  | 0  | 2  |
| Tubular basophilia<br>Minimal                | 3  | 0  | 1  | 6  | 4  | 0  | 0  | 0  | 1  |
| Liver  | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Vacuolation, midzonal, hepatocyte<br>Minimal | 0  | 0  | 4  | 5  | 7  | 0  | 0  | 0  | 0  |
| Mild   | 0  | 0  | 0  | 3  | 3  | 0  | 0  | 0  | 0  |
| Vacuolation, biliary, focal<br>Minimal       | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 6  | 7  |
| Mild   | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 4  | 1  |
| Hypertrophy, centrilobular<br>Minimal        | 0  | 0  | 3  | 2  | 3  | 0  | 0  | 5  | 7  |
| Mild   | 0  | 0  | 0  | 6  | 4  | 0  | 0  | 0  | 1  |
| Moderate                                     | 0  | 0  | 0  | 2  | 3  | 0  | 0  | 0  | 0  |
| Lungs  | 10 | 1  | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Vacuolation, alv. macrophage<br>Minimal      | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 2  | 5  |
| Mild   | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 6  | 1  |
| Necrosis, mucosal<br>Mild                    | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 1  |
| Hypertrophy, medial<br>Mild                  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 1  |
| Hyperplasia, epithelial<br>Mild              | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  | 0  |
| Hemorrhage, alveolar<br>Minimal              | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 2  |
| Fibrosis, lumen, bronchial<br>Minimal        | 0  | 0  | 2  | 0  | 0  | 0  | 0  | 0  | 0  |
| Mild   | 0  | 0  | 1  | 1  | 0  | 0  | 1  | 0  | 0  |
| Fibrosis, pleural – mild                     | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  | 0  |
| Eosinophilia, alveolar wall<br>Mild          | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 2  |
| Congestion<br>Minimal                        | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  | 0  |
| Mild   | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 2  |
| Moderate                                     | 0  | 1  | 0  | 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 |
| Vacuolation, epithelium        |    |   |    |    |    |    |    |    |
| Minimal                        | 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 |
| 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 |
| Vacuolation, endometrium, macr |    |   |    |    |    |    |    |    |
| Minimal                        |    |   |    |    | 0  | 0  | 0  | 1  |
| Vacuolation, epithelium        |    |   |    |    |    |    |    |    |
| mild                           |    |   |    |    | 0  | 0  | 0  | 0  |

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.

| Dose group                   | Gender | TK Parameter                |                 |              |
|------------------------------|--------|-----------------------------|-----------------|--------------|
|                              |        | AUC (0-24 hr)<br>(ng.hr/ml) | Cmax<br>(ng/ml) | Tmax<br>(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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| 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 0.1 ng/ml   |
| Other:              | Physical exam (body temperature, heart rate and blood pressure):<br>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.

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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 vacuolation, 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 noted 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 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)<br>(ng.hr/ml) | Cmax<br>(ng/ml) | Tmax<br>(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          |

**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 ( $AUC_{0-24 \text{ hr}}$ ) 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 ( $AUC_{0-24 \text{ hr}}$ ) 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

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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 — 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 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.

## 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. 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

**Key findings:** SCH 34117 with added degradants 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

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

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degradants \_\_\_\_\_  
\_\_\_\_\_ 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  
\_\_\_\_\_  
\_\_\_\_\_

**Key findings:** SCH 34117 with added degradants \_\_\_\_\_  
\_\_\_\_\_ 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:** \_\_\_\_\_

**Study type:** In vivo mouse micronucleus

**Volume #, and page #:** 6, 87

**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 \_\_\_\_\_ lded degradants: \_\_\_\_\_

\_\_\_\_\_; Batch No.: \_\_\_\_\_

**Formulation/vehicle:** ( \_\_\_\_\_ aqueous methylcellulose

**Methods:**

Strains/species/cell line: Mouse \_\_\_\_\_); 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: \_\_\_\_\_ aqueous methylcellulose

Negative controls: \_\_\_\_\_ aqueous methylcellulose

Positive controls: cyclophosphamide

Comments: selected controls are adequate

Exposure conditions: Mice received two consecutive daily ip doses.

## Doses used in definitive study:

| Dose group  | Dose (mg/kg/day) | # 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; compared 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.

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**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  $\frac{1}{10}$  in the drug product.

**Labeling recommendations:**

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

## 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 studied 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 vertebra, 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<sub>1</sub> pup survival, pre-weaning growth or F<sub>1</sub> 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<sub>2</sub> 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.

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**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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**X. APPENDIX/ATTACHMENTS:**

**Addendum to review:**

NDA 21-165 Original Review

NDA 21-165 Label Review #1

Addendum to NDA 21-165 Label Review #1

IND 58,506 Original Review

IND 58,506 Review #2

**Other relevant materials (Studies not reviewed, appended consults, etc.):** None

**Any compliance issues:** None

**Note: The page numbers on the attached reviews do not reflect the original page numbers of these reviews.**

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**DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS**  
**REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA**  
Original Review

KEY WORDS: Anti-histamine

NDA No. 21-165

**Dates and content of submission:** 20 OCT 1999: Original submission  
20 MAR 2000  
19 APR 2000

**Reviewer:** Timothy J. McGovern, Ph.D. **Review Completed:** 29 SEP 2000

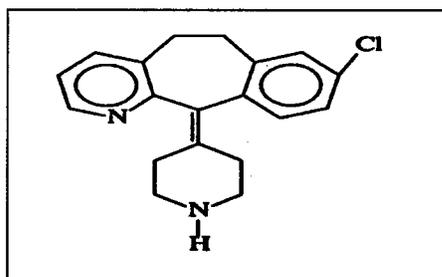
**Information to be Conveyed to Sponsor:** Yes (✓), No ( )

**Sponsor:** Schering Plough Corp., Kenilworth, NJ, USA

**Drug Name:** *Generic:* Descarboethoxyloratadine (DCL); 5 mg tablet  
*Code Name:* SCH 34117  
*Commercial:* CLARINEX

**Chemical name:** 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)

**Structure:**



**Empirical Formula:** C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>

**Molecular Weight:** 310.82

**Drug Class:** Anti-histamine

**Indication:** Seasonal allergic rhinitis

**Proposed Clinical Dose:** 5 mg once daily in adults and children 12 years of age and older. In a 50 kg adult this is 0.25 mg/kg or 6.2 mg/m<sup>2</sup>.

**Drug Product Formulation: 5 mg tablet**

| Ingredient                              | Core tablet (mg) |
|---|------------------|
| Desloratadine                           | 5                |
| Corn starch, NF                         |                  |
| Dibasic calcium phosphate dihydrate USP |                  |
| Microcrystalline cellulose NF           |                  |
| Talc USP                                |                  |
| <del>Blue</del>                         |                  |
| <del>[ Clear</del>                      |                  |
| Carnauba wax NF                         |                  |
| White wax NF                            |                  |
| <del></del>                             |                  |
| <del></del>                             |                  |

Total tablet weight 106.61

a: evaporates during manufacturing. b: Sublimes during manufacturing.

**Route of Administration:** Oral (tablet)

**Related INDs/NDAs:**

IND 55,364 – descarboethoxyloratadine tablets

IND ~~\_\_\_\_\_~~

IND ~~\_\_\_\_\_~~

NDA 19-658

NDA 20-704

**Previous Review(s), Date(s) and Reviewer(s):** This NDA has not been reviewed previously. Relevant reviews of related INDs and NDAs are listed below.

IND 55,364: Descarboethoxyloratadine tablets

Original review by Dr. T. McGovern (May 22, 1998)

Review #2 by Dr. T. McGovern (October 27, 1998)

Review #3 by Dr. T. McGovern (December 15, 1998)

Review #4 by Dr. T. McGovern (January 31, 2000)

Review #5 by Dr. T. McGovern (June 7, 2000)

NDA 19658: Loratadine tablets

Original review by B.C.Y. Tai (October 30, 1987)

**Preclinical Studies Submitted and Reviewed in this NDA:**

| Study  | Res. Report #/<br>Reference # | Vol. |
|--|-------------------------------|------|
| <b><i>New Pharmacology – Schering Study Reports:</i></b>   |                               |      |
| Inhibition of <sup>3</sup> H-pyrimidine binding to the histamine H <sub>1</sub> -receptor by loratadine  | SN 30372                      | 1.7  |
| Inhibition of <sup>3</sup> H-pyrimidine binding to the histamine H <sub>1</sub> -receptor by desloratadine (SCH 34117) and other loratadine metabolites  | SN 30279                      | 1.7  |
| Topical antihistamine activity of loratadine, SCH 34117 and levocabastine  | D-27083                       | 1.7  |
| biochemical assays report  | D-28718                       | 1.7  |
| Effect of SCH 34117 on tumor necrosis factor $\alpha$ production.  | D-28727                       | 1.7  |
| Inhibition of cytokine generation and mediator release by human basophils treated with desloratadine   | SN 30853                      | 1.7  |
| Descarboethoxyloratadine (DCL) and eosinophil chemotaxis and adhesion to endothelial cells, and production of superoxide anions and leukotriene C <sub>4</sub> from human blood eosinophils.   | SN 30854                      | 1.8  |
| Antitussive activity of desloratadine (SCH 34117, DCL) and loratadine in the guinea pig  | D-30053                       | 1.8  |
| Effects of desloratadine (SCH 34117, DCL) and loratadine on nasal congestion in the cat  | D-30026                       | 1.8  |
| The effect of oral SCH 34117 on the response to <i>Ascaris</i> challenge in allergic cynomolgus monkeys.   | D-28686                       | 1.8  |
| <b><i>New Pharmacology – Publications and References:</i></b>  |                               |      |
| Kleine-Tebbe J, Josties C, Frank G et al. Inhibition of IgE and non-IgE-mediated histamine release from human basophil leukocytes in vitro by a histamine H <sub>1</sub> -antagonist, desethoxycarbonyl-loratadine. <i>J Allergy Clin Immunol.</i> 1994; 93: 494-500.                    | 1                             | 1.7  |
| Berthon B, Taudou G, Cobettes L et al. In vitro inhibition by loratadine and descarboethoxyloratadine of histamine release from human basophils and of histamine release and intracellular calcium fluxes in rat basophilic leukemia cells. <i>Biochem Pharmacol.</i> 1994; 47: 789-794. | 2                             | 1.7  |
| Genovese A, Patella V et al. Loratadine and desethoxycarbonylloratadine inhibit the immunological release of mediators from human Fc $\epsilon$ RI+ cells. <i>Clin Exp Allergy.</i> 1997; 27: 559-567.   | 3                             | 1.7  |
| Lippert M, Kruger-Krasagakes S et al. Pharmacological modulation of IL-6 and IL-8 secretion by the H <sub>1</sub> -antagonist descarboethoxyloratadine and dexamethasone by human mast and basophil cell lines. <i>Exp Dermatol.</i> 1995; 4: 272-276                                    | 4                             | 1.7  |
| Lebel B, Bousquet J et al. Loratadine reduces RANTES release by an epithelial cell line. <i>J Allergy Clin Immunol.</i> 1997; 99: S44 (abstract).  | 5                             | 1.7  |
| Paubert-Braquet M and Czarlewski W. Effect of loratadine and SCH 34117 on superoxide anion production from human polymorphonuclear neutrophils and monocytes. <i>J Allergy Clin Immunol.</i> 1994; 93: 257 (abstract).   | 6                             | 1.7  |
| Molet S, Gosset P et al. Inhibitory activity of loratadine and descarboethoxyloratadine on histamine-induced activation of endothelial cells. <i>Clin Exp Allergy.</i> 1997; 27: 1167-1174.  | 7                             | 1.7  |
| <b><i>New Safety Pharmacology Studies and Publications:</i></b>  |                               |      |
| Ancillary pharmacology of SCH 34117  |                               |      |
| Effects of loratadine metabolites on cardiovascular function in rats   | SN 30063                      | 1.8  |
| Electrocardiographic effects of intravenous SCH 34117 in the guinea pig  | P-5429                        | 1.8  |
| The comparative effects of quinidine and non-sedating antihistamines on HERG (I Kr) channels expressed in <i>Xenopus</i> oocytes.  | D-28578                       | 1.8  |
| One-week oral (gavage) cardiovascular study of SCH 34117 in cynomolgus monkeys   | D-28717                       | 1.8  |
| A.E. Lacerda, M-L. Roy, E.W. Lewis and D. Rampe. Interactions of the non-sedating antihistamine loratadine with a Kv1.5 type potassium channel cloned from human heart. <i>Mol. Pharmacol.</i> 52, 314-322, 1997   | SN 98558                      | 1.10 |
| Effects of Sch 34117 on respiratory function in conscious rats.  | 8                             | 1.8  |
| <b><i>New Pharmacokinetic (ADME) Studies:</i></b>  |                               |      |
| SCH 34117: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 34117 following a   | SN 30650                      | 1.8  |

| Study   | Res. Report #/<br>Reference # | Vol.         |
|---|-------------------------------|--------------|
| single oral dose to male and female mice:   | SN 97308                      | 1.36         |
| SCH 29851: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 29851 following a single oral dose to male and female mice.                                  | SN 97311                      | 1.37         |
| SCH 29851: A 3-week toxicokinetic study with SCH 29851 administered as a drug-diet mixture to male and female mice.   | SN 99076                      | 1.39         |
| SCH 34117: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 34117 following a single oral or intravenous dose to male and female albino rat.             | SN 97307                      | 1.40         |
| SCH 29851: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 29851 following a single oral dose to the male and female albino rat.                        | SN 97310                      | 1.42         |
| One week oral (gavage) toxicokinetic study of SCH 34117 and loratadine (SCH 29851) in rats.   | P-6938                        | 1.45         |
| SCH 29851: A three week toxicokinetic study of SCH 29851 administered as a drug-diet mixture to male and female rats.   | SN 99077                      | 1.46         |
| A three week toxicokinetic study with SCH 29851 or SCH 34117 administered orally to male and female rats.   | SN 99078                      | 1.47         |
| SCH 34117: A two week toxicokinetic study with SCH 29851 or SCH 34117 administered orally to female New Zealand white rabbits.  | SN 99080                      | 1.49         |
| SCH 34117: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 34117 following a single oral or intravenous dose to the male and female cynomolgus monkeys. | SN 97309/<br>SN98452          | 1.51         |
| SCH 29851: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 29851 following a single oral dose to the male and female cynomolgus monkeys.                | SN 97312/<br>SN 98452         | 1.53         |
| SCH 34117: Toxicokinetic study of single oral (gavage) dose of SCH 34117 or SCH 29851 in cynomolgus monkeys.  | P-6815                        | 1.55         |
| SCH 34117: A three week toxicokinetic study of SCH 29851 or SCH 34117 administered orally to male and female cynomolgus monkeys.  | SN 99079                      | 1.56         |
| SCH 34117: In vitro binding of SCH 34117 to mouse, rat, monkey and human plasma proteins using ultrafiltration.   | SN 99215                      | 1.58         |
| In vitro metabolism of SCH 29851 and SCH 34117 by rat, mouse, monkey, rabbit and human using hepatocytes, tissue slices and/or microsomes.                                | SN 97304                      | 1.58         |
| Interim report: In vitro metabolism of SCH 29851 and SCH 34117 in rat and mouse liver microsomes and S( fractions from normal and Aroclor-treated animals.                | SN 97304                      | 1.58         |
| <b><i>New Genetic Toxicology Studies:</i></b>   |                               |              |
| Bacterial mutagenicity study of SCH 34117 with impurities and degradants  |                               |              |
| Chromosome aberration study of SCH 34117 with impurities and degradants in human peripheral blood lymphocytes   | SN 99287<br>SN 99241          | 10.8<br>10.8 |
| <b><i>New Reproductive Toxicology:</i></b>  |                               |              |
| Oral (gavage) fertility study of SCH 34117 in rats  |                               |              |
| Fertility study of SCH 34117 administered by oral gavage in male rats   | P-6891                        | 1.28         |
| Oral (gavage) embryo-fetal developmental toxicity and toxicokinetic study in rats   | SN 98552                      | 1.29         |
| Oral perinatal and postnatal development study of SCH 34117 in rats   | P-6922                        | 1.31         |
| Oral embryo-fetal development study of SCH 34117 in rabbits   | SN 97117<br>P-6802            | 1.33<br>1.32 |

**Previously Reviewed Preclinical Studies in IND 55,364 and Submitted in this NDA:**

| Study  | Res. Report #    | Vol. | Date of Review |
|--|------------------|------|----------------|
| <b>Pharmacology – Schering Study Reports:</b>  |                  |      |                |
| Onset of antihistamine activity of loratadine and SCH 34117.   | D-26677          | 1.7  | 5/22/1998      |
| Antihistamine activity of loratadine and SCH 34117 in cynomolgus monkeys.  | D-28097          | 1.7  | 5/22/1998      |
| Anticholinergic actions of loratadine, SCH 34117, and other antihistamines in spontaneously breathing guinea pig right atria.  | P-5950           | 1.7  | 5/22/1998      |
| <b>Pharmacology – Publications and References:</b>   |                  |      |                |
| Handley DA, McCullough JR, Fang Y et al. Descarboethoxyloratadine, a metabolite of loratadine, is a superior antihistamine. <i>Ann. Allergy Asthma and Immunol.</i> 1997; 78: 143.   |                  | 1.7  | 5/22/1998      |
| Cardelus, Puig J, Bou J et al. Xerostomia and mydriasis; two possible muscarinic peripheral side effects associated with descarboethoxyloratadine, the main metabolite of loratadine. <i>Proc Br Pharmacol Soc.</i> 1997; P149.  |                  | 1.7  | 5/22/1998      |
| Hey JA, del Prado M et al. Antihistamine activity central nervous system and cardiovascular profiles of histamine H1 antagonists: comparative studies with loratadine, terfenadine and sedating antihistamines in guinea pigs. <i>Clin Exp Allergy.</i> 1995; 25: 974-984. |                  | 1.7  | 5/22/1998      |
| I. Dacic, C. Ko, Y. Shuba and M. Morad. Comparative effects of loratadine and terfenadine on cardiac K <sup>+</sup> channels. <i>J. Cardiovasc. Pharmacol</i> 30, 42-54, 1997  |                  | 1.7  | 5/22/1998      |
| R. Caballero, E. Delpon, C. Valenzuela, M. Longobardo, L. Franqueza and J. Tamargo. Effect of descarboethoxyloratadine, the major metabolite of loratadine, on the human cardiac potassium channel Kv1.5. <i>Br. J. Pharmacol.</i> 122 796-798, 1997                       |                  | 1.7  | 5/22/1998      |
| <b>Safety Pharmacology:</b>  |                  |      |                |
| Effect of loratadine and its metabolite, descarboethoxyloratadine, on the QT interval in the isolated perfused rabbit heart model (Langendorff)  | 30523            | 1.8  | 6/7/2000       |
| Effect of desloratadine (SCH 34117) on electrophysiological properties of guinea pig ventricular muscle.   | SN 30416         | 1.8  | 6/7/2000       |
| Effect of loratadine (SCH 29851) and desloratadine (SCH 34117) on Na <sup>+</sup> current in rabbit ventricular myocytes.  | SN 30417         | 1.8  | 6/7/2000       |
| Effect of loratadine (SCH 29851) and desloratadine (SCH 34117) on I <sub>Kr</sub> and I <sub>K1</sub> .  | SN 30418         | 1.8  | 6/7/2000       |
| <b>Pharmacokinetics:</b>   |                  |      |                |
| Summary of metabolic profiling (SCH 34117 and SCH 29851) data from SPRI pilot studies in rat, mouse and monkey.  | D-28407          | 1.36 | 5/22/1998      |
| SCH 34117: Toxicokinetic study of single oral (gavage) dose of SCH 34117 or SCH 29851 in cynomolgus monkeys.   | P-6527           | 1.55 | 12/15/1998     |
| SCH 34117: A study of the tissue distribution of radioactivity in male and female sprague dawley rats and male and female long evans rats following a single oral dose of <sup>14</sup> C-SCH 34117  | P-6741           |      | 6/7/2000       |
| <b>Acute Toxicology:</b>   |                  |      |                |
| Single-dose oral administration, mice  |                  |      |                |
| Single-dose intraperitoneal administration, mice   | P-6771           | 1.9  | 5/22/1998      |
| Single-dose oral administration, rats  | P-6772           | 1.9  | 5/22/1998      |
| Single-dose intraperitoneal administration, rats   | P-6769           | 1.9  | 5/22/1998      |
| Oral (gavage) rising-dose tolerance study of SCH 34117 in cynomolgus monkeys   | P-6770<br>P-6808 | 1.9  | 5/22/1998      |
| <b>Multiple Dose Toxicology:</b>   |                  |      |                |
| Two-week oral safety profile study of SCH 34117 in rats.   |                  |      |                |
| Two-week oral (gavage) range-finding toxicity and toxicokinetic study of   | D-18289          | 1.10 | 5/22/1998      |



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*Note: Portions of this review were excerpted directly from the sponsor's submission.*

**Introduction/Drug History:** Descarboethoxyloratadine (SCH 34117) is an active metabolite of loratadine, a drug product approved as Claritin in 1993 for the treatment of allergic rhinitis. The sponsor's preclinical safety evaluation program for SCH 34117 was based upon a strategy consisting of genetic toxicology, reproductive toxicology, acute and subchronic toxicology, pharmacokinetic, toxicokinetic, ADME, AME and metabolite identification studies with SCH 34117 that allow bridging to chronic preclinical toxicology studies, carcinogenicity studies and clinical safety experience with SCH 34117 obtained from studies performed with loratadine. The Division agreed that the sponsor would not be required to perform additional chronic toxicity studies with SCH 34117 based upon results of 3-month studies with SCH 34117 in rats and monkeys (see IND 55,364, Review #4). However, CDER's Senior Pharmacology/Toxicology Policy Group concluded that SCH 34117 was adequately assessed for carcinogenicity in rats in a study performed with loratadine, while a 2 year mouse carcinogenicity study with SCH 34117 should be performed as a Phase 4 commitment.

#### **PHARMACOLOGY:**

The sponsor submitted numerous study reports and nonclinical pharmacology reports from the published literature which investigated the pharmacodynamic activity of SCH 34117. These studies are summarized below.

*Mechanism of Action:* Three new studies investigating the comparative antihistamine potency of SCH 34117 and related compounds in rat brain membrane H1 receptors, and the activity of SCH 34117 at various receptor sites, were submitted and are summarized in Table 1. SCH 34117 was ~ 20-fold more potent than loratadine in rat brain H1 receptor activity and was comparable in potency to its primary unconjugated metabolites. In a separate study, SCH 34117 showed greatest activity at central H1 receptors while activity at peripheral H1 receptors was similar to that at M2 muscarinic receptors. Other receptor sites tested showed significantly reduced activity.

**Table 1. Receptor binding assays:**

| Cell/Model type                  | Report #/<br>Reference | Activity   |
|----------------------------------|------------------------|--|
| Rat brain membrane               | SN 30372               | SCH 34117 was ~ 20-fold more potent than loratadine, but comparable to chlorpheniramine, in inhibiting binding of [ <sup>3</sup> H]pyrilamine to rat brain H1 receptor.<br>Ki = 4.8, 86 and 3.7 nM, respectively.  |
|                                  | SN 30279               | SCH 34117 and its hydroxylated metabolites showed similar potency in inhibiting binding of [ <sup>3</sup> H]pyrilamine to rat brain H1 receptor while the conjugated glucuronide of the 3-OH-DCL metabolite displayed reduced potency by over 100-fold.<br><u>Compound</u> <u>Ki (nM)</u><br>SCH 34117 DCL 7.0<br>SCH 39090 6-OH DCL 4.5<br>SCH 39091 5-OH DCL 9.5<br>SCH 45581 3-OH DCL 13<br>SCH 354202 3-OH DCL gluc 19% at 2 $\mu$ M |
| Various species target receptors | D-28718                | <u>Receptor type</u> <u>IC50 (nM)</u> <u>Ki (nM)</u><br>Histamine H1, central 17 5.7<br>Histamine H1, peripheral 168 13<br>Histamine, H2 360 353<br>Muscarinic M1 208 50<br>Muscarinic M2 131 47<br>Muscarinic M4 493 104<br>Muscarinic M5 445 320<br>Serotonin 5-HT7 369 204  |

*Drug Activity Related to Proposed Indication:* Antiallergic and antiinflammatory effects of SCH 34117 have been demonstrated in numerous *in vitro* and *in vivo* tests submitted to the NDA. The results of *in vitro* tests in human cells or cell lines are summarized in Table 2. SCH 34117 inhibited superoxide anion production by PMN, histamine induced activation of endothelial cells, P-selectin expression, release of IL-4, IL-6, IL-8 and IL-13, release of histamine, tryptase, LTC4 and PGD2, release of RANTES, and attenuated eosinophil chemotaxis and adhesion. Weak inhibitory activity of TNF-a was also observed.

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**Table 2.** *In vitro* studies assessing the effects of SCH 34117 on mediator release and chemotaxis.

| Cell/Model type   | Report #/<br>Reference | Activity   |
|---|------------------------|--|
| Inhibition of superoxide production in human polymorpho-nuclear neutrophils and monocytes   | Ref. 6                 | SCH 34117, but not loratadine, inhibited superoxide anion production by PMN induced by fMLP or PAF at > 1 $\mu$ M with almost complete inhibition at 50 $\mu$ M.<br>Both drugs inhibited superoxide anion production by monocytes induced by PMA or zymosan at > 0.1 and 1 $\mu$ M, respectively.<br>Effective concentrations are greater than those required to block H1 receptors suggesting response is unrelated to receptor interaction.  |
| Inhibition of endothelial cell activation, P-selectin expression and IL-6 and IL-8 in human umbilical vein endothelial cells                                  | Ref. 7                 | SCH 34117 and loratadine inhibited histamine-induced ( $10^{-4}$ M) activation of endothelial cells:<br>Similar inhibition of P-selectin expression (IC <sub>50</sub> = $13 \times 10^{-9}$ M and $23 \times 10^{-9}$ M, respectively).<br>IL-6 and IL-8 inhibition: SCH 34117 displayed greater potency (IC <sub>50</sub> = $2.6 \times 10^{-12}$ M and $10^{-9}$ M, respectively) than loratadine (IC <sub>50</sub> = $0.3 \times 10^{-6}$ M and $0.2 \times 10^{-6}$ M, respectively)                       |
| Inhibition of chemotaxis, and leukotriene and superoxide production in human eosinophils and secretion of interleukins and TNF- $\alpha$ by monocytes         | SN 30854               | Eosinophils: Attenuated chemotaxis in response to PAF with maximum attenuation of 36% at 10 $\mu$ M and adhesion (25% at 10 $\mu$ M). No effect noted on leukotriene production at a concentration of 10 $\mu$ M. 10 $\mu$ M inhibited PMA-stimulated and spontaneous superoxide generation<br>Monocytes: SCH 34117 (100 nM to 10 $\mu$ M) did not inhibit secretion of IL-4, -5, -13, -10, -1B, -16 and TNF- $\alpha$ by PBMC.  |
| Inhibition of histamine release in leukocytes from allergic and nonallergic subjects  | 1                      | IgE-mediated and calcium ionophore A23187-induced histamine release inhibited by SCH 34117 in dose-dependent fashion (IC <sub>30</sub> = 6-11 $\mu$ mol/L).<br>Higher SCH 34117 concentrations induced mediator release.<br>Rapid onset of inhibition at 10 $\mu$ mol/L.   |
| Inhibition of histamine release in human basophils and rat basophilic leukemia cells  | 2                      | Dose-dependent inhibition of histamine release observed at doses above 2 $\mu$ M SCH 34117 and 7 $\mu$ M loratadine in anti-IgE triggered human basophils and DNP-triggered rat basophilic leukemia cells.<br>Inhibition by loratadine increased when extracellular Ca <sup>2+</sup> reduced from 1.8 to 0.45 $\mu$ M.<br>Both drugs (2.5-25 $\mu$ M) inhibited the cytosolic Ca <sup>2+</sup> rise induced by DNP-BSA challenge in rat cells which may inhibit mediator release.                              |
| Inhibition of histamine, LTC <sub>4</sub> , PGD <sub>2</sub> and tryptase release in human Fc $\epsilon$ RI+ cells from peripheral blood, skin or lung tissue | 3                      | SCH 34117 and loratadine ( $3 \times 10^{-6}$ to $10^{-4}$ M) inhibited release of histamine and LTC <sub>4</sub> (5-40%) following pre-incubation before Der p 1 antigen or anti-Fc $\epsilon$ RI challenge.<br>10-40% inhibition of histamine and LTC <sub>4</sub> and PGD <sub>2</sub> release from lung tissue cells activated by anti-Fc $\epsilon$ RI.<br>10-40% inhibition of histamine, tryptase, LTC <sub>4</sub> and PGD <sub>2</sub> release from skin cells challenged with anti-Fc $\epsilon$ RI. |
| Inhibition of IL-6 and IL-8 release in human mast cell line (HMC-1) and basophilic cell line (KU812)  | 4                      | SCH 34117 ( $10^{-14}$ to $10^{-5}$ M) dose-dependently suppressed IL-6 release by up to 40% and IL-8 release by up to 50% after 1 hr preincubation followed by PMA and Ca-ionophore A23187 stimulation.<br>Dexamethasone ( $10^{-11}$ to $10^{-6}$ M) inhibited release by 60-80%.  |
| Inhibition of TNF- $\alpha$ production in human peripheral blood cells  | D-28727                | Weak inhibitory activity against TNF- $\alpha$ production (7-24% at 0.1 to 10 $\mu$ M) following LPS-stimulation. Rolipram significantly more potent (IC <sub>50</sub> = 0.035-0.12 $\mu$ M).  |
| Inhibition of RANTES release in nasal polyp   | 5                      | SCH 34117 and loratadine (10 $\mu$ m, added 15 minutes prior to activation) significantly reduced RANTES release (~ 70% and 40%, respectively)   |

|   |         |  |
|---|---------|--|
| epithelial cell line                                      |         | induced by TNF- $\alpha$ . Spontaneous RANTES release was not significantly affected.  |
| Inhibition of IL-4 and IL-13 secretion in human basophils | D-30853 | SCH 34117 (10 <sup>-7</sup> to 10 <sup>-5</sup> M) 6-7 times more potent in preventing secretion of IL-4 (~18-90%) and IL-13 induced by anti-IgE than at inhibiting histamine (~2-50%) and LTC <sub>4</sub> release (0-50%). Cytokines equally inhibited following activation with ionomycin although there was no effect on histamine release. Lesser effect inhibiting IL-13 secreted in response to IL-3 and PMA, suggesting the drug targets individual paths of cytokine generation. IL-4 mRNA accumulation inhibited up to 80% following pretreatment with SCH 34117, suggesting drug also targets signals regulating cytokine gene transcription. |

*In vivo* functional assays are summarized in Table 3. SCH 34117 was more potent than loratadine in inhibiting the guinea pig nasal response to histamine challenge and in inhibiting cough in ovalbumin sensitized guinea pigs. In monkeys, SCH 34117 reduced the bronchospasm and associated increase in airway resistance and decrease in compliance induced by allergen challenge and histamine induced bronchospasm. No effect on decongestion was noted in cats.

**Table 3.** *In vivo* functional assays.

| Model  | Reference                   | Activity   |          |                             |                             |               |       |               |           |     |               |            |     |                |
|--|-----------------------------|--|----------|-----------------------------|-----------------------------|---------------|-------|---------------|-----------|-----|---------------|------------|-----|----------------|
| Inhibition of nasal response to histamine challenge in anesthetized guinea pig | D-27083                     | Levocabastine >>>SCH 34117 >>loratadine in inhibiting nasal response (increase in microvascular permeability) to histamine challenge; SCH 34117 10-fold more potent than loratadine.<br><table border="1"> <thead> <tr> <th>Compound</th> <th>ED<sub>50</sub> (<math>\mu</math>g)</th> <th>Max. efficacy/concentration</th> </tr> </thead> <tbody> <tr> <td>Levocabastine</td> <td>0.025</td> <td>85%/1 <math>\mu</math>g</td> </tr> <tr> <td>SCH 34117</td> <td>0.9</td> <td>69%/3 <math>\mu</math>g</td> </tr> <tr> <td>Loratadine</td> <td>8.7</td> <td>49%/10 <math>\mu</math>g</td> </tr> </tbody> </table> | Compound | ED <sub>50</sub> ( $\mu$ g) | Max. efficacy/concentration | Levocabastine | 0.025 | 85%/1 $\mu$ g | SCH 34117 | 0.9 | 69%/3 $\mu$ g | Loratadine | 8.7 | 49%/10 $\mu$ g |
| Compound   | ED <sub>50</sub> ( $\mu$ g) | Max. efficacy/concentration  |          |                             |                             |               |       |               |           |     |               |            |     |                |
| Levocabastine  | 0.025                       | 85%/1 $\mu$ g  |          |                             |                             |               |       |               |           |     |               |            |     |                |
| SCH 34117  | 0.9                         | 69%/3 $\mu$ g  |          |                             |                             |               |       |               |           |     |               |            |     |                |
| Loratadine   | 8.7                         | 49%/10 $\mu$ g   |          |                             |                             |               |       |               |           |     |               |            |     |                |
| Inhibition of capsaicin-induced cough in guinea pigs                           | SN 30053                    | SCH 34117 and loratadine (10 mg/kg, po, each) did not attenuate the number of coughs induced by aerosolized capsaicin. Both inhibited cough in ovalbumin sensitized guinea pigs with a minimum effective dose of 0.3 and 1 mg/kg, po, respectively.  |          |                             |                             |               |       |               |           |     |               |            |     |                |
| Effect on compound 48/80-induced congestion                                    | SN 30026                    | Neither SCH 34117 nor loratadine (3 mg/kg, iv) displayed decongestant effects on congestion induced by aerosolized compound 48/80.   |          |                             |                             |               |       |               |           |     |               |            |     |                |
| Effect on allergen- and histamine-induced bronchospasm in monkeys              | D-28686                     | SCH 34117 (5 mg/kg, po) reduced allergen-induced bronchospasm, heightened resistance (~60%) and reduced compliance (~20%) and histamine induced bronchospasm (normal and allergic monkeys). No effect was noted after 24 hours on allergen-induced increase in BAL cells.  |          |                             |                             |               |       |               |           |     |               |            |     |                |

Collectively, the submitted pharmacodynamic studies suggest that SCH 34117, like its parent drug loratadine, may have therapeutic value in treating seasonal allergic rhinitis in humans.

**SAFETY PHARMACOLOGY:**

The results of new safety pharmacology studies submitted to this NDA are summarized in Table 4. SCH 34117 induced no significant in vivo cardiovascular effects in rats or monkeys (doses up to 12 mg/kg, oral, or 10 mg/kg, intraperitoneal) or in guinea pigs (25 mg/kg, IV). In vitro assessments showed that SCH 34117 was ~ 7-fold less potent than loratadine in blocking KV1.5 channel in HEK 293 cells and loratadine (10  $\mu$ M) failed to significantly alter HERG currents. Loratadine and SCH 34117 (up to 10  $\mu$ M) had minimal effects on  $I_{HERG}$  current (15-20%) compared to terfenadine and quinidine (IC<sub>50</sub> = 82 and 168 nM, respectively). SCH 34117 had no effect on the gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg in rats.

**Table 4.** Summary of safety pharmacology studies.

| Model  | Study # / Reference # | Results  |
|--|-----------------------|--|
| Cardiovascular effects<br>Conscious,<br>normotensive rats  | P-5429                | IP administration (10 mg/kg) of loratadine, and metabolites SCH 34117, SCH 39091 and SCH 45581: No significant effects on blood pressure or heart rate for up to 3 hours after dosing.   |
|  | SN 30650              | Single oral SCH 34117 dose (4 or 12 mg/kg): No effect on minute volume, respiratory frequency and tidal volume for 8 hours after treatment.  |
| Cynomolgus monkeys   | SN 30063              | Rats: SCH 34117 (4 or 12 mg/kg, po) no significant change in blood pressure, PR, QRS, QT or QTc; moderate increase in heart rate (+33 bpm) at 6 hr postdosing at 12 mg/kg.   |
|  | SN 30063              | Monkeys: SCH 34117 (12 mg/kg): moderate increase in heart rate at 4 hr postdosing, non-significant widening of QRS interval (11% over basal value). QT significantly shortened, but QTc not affected.  |
|  | SN 98558              | SCH 34117 (0, 4 or 12 mg/kg/day, po) administered for 7 days: No test article-related changes in diastolic, systolic or mean arterial blood pressure, heart rate, waveform magnitude, or timing of events (PR, QRS, QT or QTc intervals). No cardiac arrhythmias occurred. NOAEL for cardiovascular effects = 12 mg/kg<br><u>Plasma levels:</u><br>Males Day 0: 50.3 ng/ml at 4 mg/kg; 456 ng/ml at 12 mg/kg;<br>Day 6: 84.1 ng/ml at 4 mg/kg; 1041 ng/ml at 12 mg/kg;<br>Females Day 0: 153 ng/ml at 4 mg/kg, 199 ng/ml at 12 mg/kg.<br>Day 6: 193 ng/ml at 4 mg/kg, 267 ng/ml at 12 mg/kg. |
| Anesthetized guinea pig  | D-28578               | IV administration of SCH 34117 (25 mg/kg): No effects on blood pressure or heart rate for up to 30 minutes after dosing. Mean plasma concentration ranged from 451 ng/ml (60 minutes) to 1165 ng/ml (1 minute).  |
| HEK 293 and mouse<br>Ltk- cell lines<br>transfected with human<br>cardiac Kv1.5K+<br>channel complementary | Ref. 8                | HEK 293 cells: SCH 34117 ~ 7-fold less potent than loratadine in blocking Kv1.5 channel (IC <sub>50</sub> = 5.6x10 <sup>-6</sup> M vs 8.08x10 <sup>-7</sup> M) at +50 mV). Loratadine enhanced the rate of Kv1.5 current decay and block was enhanced at membrane potentials near threshold relative to higher potentials but did not alter the kinetics of Kv1.5 current activation or  |

|  |          |  |
|--|----------|--|
| DNA, HERG cardiac K <sup>+</sup> channels from <i>X. laevis</i> oocyte     |          | deactivation.<br>Mouse Ltk <sup>-</sup> : Loratadine (3 μM) reduced the mean probability of Kv1.5 channel opening by reducing the number of openings in bursts and burst duration.<br>HERG K <sup>+</sup> : Loratadine (10 μM) failed to significantly alter HERG currents over wide range of test potentials. |
| Human HERG (I <sub>Kr</sub> ) channels expressed in <i>Xenopus</i> oocytes | D-28717  | Loratadine and SCH 34117 (up to 10 μM) had minimal effects on I <sub>HERG</sub> current (15-20%) compared to terfenadine and quinidine (IC <sub>50</sub> = 82 and 168 nM, respectively).<br>Relative potency at 1 μM: terfenadine > quinidine > ebastine > loratadine = SCH 34117                              |
| <b>CNS:</b><br>Rats  | SN 30063 | SCH 34117 (4 or 12 mg/kg, po): minor non-significant changes 2 hr after dosing in transfer reactivity, body elevation, limb position, changes in gait and respiration in 1 of 6 rats administered 12 mg/kg.  |
| <b>Gastrointestinal:</b><br>Rat  | SN 30063 | SCH 34117 (4 or 12 mg/kg, po): caused no erosive lesions in the gastric mucosa and did not affect gastric emptying, and intestinal transit at 7.5 hr post-dosing.  |
| <b>Renal:</b><br>Rat   | SN 30063 | Renal: SCH 34117 (4 or 12 mg/kg, po): No effect on urinary excretion of Na <sup>+</sup> or K <sup>+</sup> up to 24 hr post-dosing in rats.   |

#### PHARMACOKINETICS AND TOXICOKINETICS:

**Single dose:** New pharmacokinetic studies assessing systemic exposure to both SCH 34117 and SCH 29851 (loratadine) following oral or intravenous administration in rats, monkeys and mice were submitted to the NDA by the sponsor and are summarized in Table .

Following administration of 6.5 mg/kg <sup>14</sup>C-SCH 34117, po or IV, in albino rats, the drug was generally well absorbed with higher exposures noted in females, which displayed greater oral bioavailability (Table 5). Maximum concentration was achieved within 8 hours of dosing. A higher first pass metabolism was indicated in males which displayed a higher CL/F than CL. Similarly, SCH 34117 was associated with 39% of the total circulating radioactivity in females and only ~ 12% in males suggesting a more extensive bio-transformation in the latter.

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**Table 5.** Pharmacokinetics in rats following single dose of 6.5 mg/kg SCH 34117.

| Parameters                | Oral administration       |         |           |         |      |
|---------------------------|---------------------------|---------|-----------|---------|------|
|                           | Radioactivity             |         | SCH 34117 |         |      |
|                           | Males                     | Females | Males     | Females |      |
| Cmax (ng equiv/ml)        | 807                       | 504     | 132       | 291     |      |
| Tmax (hr)                 | 6                         | 8       | 3         | 8       |      |
| AUC (tf) (ng equiv.hr/ml) | 11919                     | 8492    | 1047      | 3500    |      |
| T1/2 (hr)                 | NA                        | NA      | 2.05      | 2.83    |      |
| F (%)                     | NA                        | NA      | 45        | 94      |      |
| Fa (%)                    | 74                        | 82      | NA        | NA      |      |
| Cl/F (L/hr.kg)            | NA                        | NA      | 6.63      | 1.99    |      |
| Parameters                | IV administration         |         |           |         |      |
|                           | Cmax (ng equiv/ml)        | 1027    | 889       | 569     | 583  |
|                           | Tmax (hr)                 | 3       | 0.25      | 0.25    | 0.25 |
|                           | AUC (tf) (ng equiv.hr/ml) | 15890   | 10046     | 2300    | 3637 |
|                           | T1/2 (hr)                 | NA      | NA        | 2.26    | 2.53 |
|                           | Varea (L/kg)              | NA      | NA        | 9.63    | 6.8  |
|                           | CL (L.hr/kg)              | NA      | NA        | 2.96    | 1.86 |

Oral administration of 8 mg/kg <sup>14</sup>C-SCH 29851 in rats resulted in a plasma AUC of SCH 34117 that was 8 to 20-fold greater than parent drug and the elimination half-life was 6 to 11-fold longer (Table 6). Systemic exposure to SCH 34117 was similar to that following oral administration of 6.5 mg/kg SCH 34117. Maximum concentration was achieved within 3 hours of dosing. Thus, the study shows that SCH 29851 is extensively metabolized to SCH 37114.

**Table 6.** Pharmacokinetics in rats following single dose of 8 mg/kg SCH 29851.

| Parameters                | Oral administration |         |           |         |           |         |
|---------------------------|---------------------|---------|-----------|---------|-----------|---------|
|                           | Radioactivity       |         | SCH 29851 |         | SCH 34117 |         |
|                           | Males               | Females | Males     | Females | Males     | Females |
| Cmax (ng equiv/ml)        | 1030                | 775     | 73.1      | 42.1    | 141       | 261     |
| Tmax (hr)                 | 2                   | 82      | 1         | 0.5     | 2         | 3       |
| AUC (tf) (ng equiv.hr/ml) | 18863               | 13028   | 200       | 136     | 1523      | 2661    |
| T1/2 (hr)                 |                     |         | 2.04      | 1.71    | 13.2      | 18.8    |
| Cl/F (L/hr.kg)            |                     |         | 38.5      | 57.3    |           |         |

In the cynomolgus monkey, a similar dose of <sup>14</sup>C-SCH 34117 (6.5 mg/kg, po or IV) resulted in a systemic exposure to SCH 34117 that was similar to the rat, although a gender difference was not observed (Table 7). Oral bioavailability was ~ 51%, and a high area of distribution and long elimination half-life were observed. Similar to the rat, extensive biotransformation was noted as approximately 17% of the total radioactivity was SCH 34117. Maximum concentration was achieved within 4 hours following oral dosing.

**Table 7.** Pharmacokinetics in monkeys following single dose of 6.5 mg/kg SCH 34117.

| Parameters                | Oral administration       |         |          |           |         |          |       |
|---------------------------|---------------------------|---------|----------|-----------|---------|----------|-------|
|                           | Radioactivity             |         |          | SCH 34117 |         |          |       |
|                           | Males                     | Females | Combined | Males     | Females | Combined |       |
| Cmax (ng equiv/ml)        | 1957                      | 1476    | 1668     | 206       | 266     | 242      |       |
| Tmax (hr)                 | 4                         | 2.67    | 3.2      | 4         | 2       | 2.8      |       |
| AUC (tf) (ng equiv.hr/ml) | 24534                     | 14184   | 18324    | 2639      | 2390    | 2490     |       |
| T1/2 (hr)                 |                           |         |          | 11.3      | 8.25    | 9.46     |       |
| F (%)                     |                           |         |          | 57.1      | 47.1    | 51.1     |       |
| Fa (%)                    | 105                       | 78.5    | 89.2     |           |         |          |       |
| Cl/F (L/hr.kg)            |                           |         |          | 2.7       | 12      | 8.29     |       |
| Parameters                | IV administration         |         |          |           |         |          |       |
|                           | Cmax (ng equiv/ml)        | 1409    | 1653     | 1531      | 704     | 1073     | 888   |
|                           | Tmax (hr)                 | 2       | 1.33     | 1.67      | 0.083   | 0.083    | 0.083 |
|                           | AUC (tf) (ng equiv.hr/ml) | 19758   | 18532    | 19145     | 3642    | 4294     | 3968  |
|                           | T1/2 (hr)                 |         |          |           | 11.2    | 11.6     | 11.4  |
|                           | Varea (L/kg)              |         |          |           | 35.4    | 39.3     | 37.3  |
|                           | CL (L/hr.kg)              |         |          |           | 2.43    | 2.58     | 2.5   |

Following a single oral dose of 8 mg/kg <sup>14</sup>C-SCH 29851 in monkeys, systemic exposure to SCH 34117 was 6-fold greater than that of the parent drug (Table 8) but about 3-fold less than when 6.5 mg/kg SCH 34117 was administered orally (Table 8). Less than 5% of the total radioactivity was associated with SCH 29851 and SCH 34117 indicating extensive further metabolism of SCH 34117 similar to that following SCH 34117 administration.

**Table 8.** Pharmacokinetics in monkeys following single dose of 8 mg/kg SCH 29851.

| Parameters                | Oral administration |         |          |           |         |          |           |         |          |
|---------------------------|---------------------|---------|----------|-----------|---------|----------|-----------|---------|----------|
|                           | Radioactivity       |         |          | SCH 29851 |         |          | SCH 34117 |         |          |
|                           | Males               | Females | Combined | Males     | Females | Combined | Males     | Females | Combined |
| Cmax (ng equiv/ml)        | 3247                | 3183    | 3215     | 40.4      | 56.1    | 48.3     | 40.5      | 107     | 73.7     |
| Tmax (hr)                 | 2                   | 2       | 2        | 1.67      | 1       | 1.33     | 3.33      | 2       | 2.67     |
| AUC (tf) (ng equiv.hr/ml) | 28873               | 22407   | 25640    | 151       | 144     | 147      | 705       | 1024    | 864      |
| T1/2 (hr)                 |                     |         |          | 7.55      | 8.38    | 7.97     | 13.9      | 7.41    | 10.7     |
| Cl/F (L/hr.kg)            |                     |         |          | 81.9      | 58.1    | 70       |           |         |          |

In mice an oral dose of 6.5 mg/kg <sup>14</sup>C-SCH 34117 was well absorbed and the plasma AUC for SCH 34117 was 34% of that for radioactivity, again indicating high metabolism (Table 9). Systemic exposure in the mouse was greater than that observed in the rat and monkey. As in the monkey, no gender related differences were noted in kinetic parameters. The maximum concentration was achieved within 4 hours following oral dosing.

**Table 9.** Pharmacokinetics in mice following single dose of 6.5 mg/kg SCH 34117.

| Parameters                           | Males | Females | Combined |
|--------------------------------------|-------|---------|----------|
| Drug-derived radioactivity in plasma |       |         |          |
| C <sub>max</sub> (ng equiv/ml)       | 519   | 542     | 505      |
| T <sub>max</sub> (hr)                | 4     | 1       | 1        |
| AUC (tf) (ng equiv.hr/ml)            | 7290  | 6941    | 7115     |
| SCH 34117 in plasma                  |       |         |          |
| C <sub>max</sub> (ng/ml)             | 319   | 310     | 278      |
| T <sub>max</sub> (hr)                | 1     | 2       | 1        |
| AUC(tf) (ng.hr/ml)                   | 2502  | 2412    | 2449     |
| T <sub>1/2</sub> (hr)                | 4.67  | 3.71    | 4.17     |
| Cl/F (L/hr.kg)                       | 2.69  | 2.88    | 2.78     |

Following oral administration of 8 mg/kg <sup>14</sup>C-SCH 29851 in mice, SCH 29851 was rapidly metabolized and accounted for < 4% of total radioactivity after 0.25 hours. The combined plasma AUC for SCH 29851 and SCH 34117 was < 5% of the AUC for radioactivity indicating that they are not the major drug-derived components (Table 10). The plasma AUC for SCH 34117 was ~ 9-fold greater than that for SCH 29851, indicating extensive further metabolism of SCH 34117 similar to that following SCH 34117 administration, and was ~ one-third of that observed following oral administration of 6.5 mg/kg SCH 34117. Maximum concentration for SCH 34117 was achieved within 3 hours following oral dosing.

**Table 10.** Pharmacokinetics in mice following single dose of 8 mg/kg SCH 29851.

| Parameters                           | Males | Females | Combined |
|--------------------------------------|-------|---------|----------|
| Drug-derived radioactivity in plasma |       |         |          |
| C <sub>max</sub> (ng equiv/ml)       | 2134  | 1879    | 1817     |
| T <sub>max</sub> (hr)                | 0.5   | 1       | 0.5      |
| AUC (tf) (ng equiv.hr/ml)            | 15120 | 19910   | 17560    |
| SCH 29851 in plasma                  |       |         |          |
| C <sub>max</sub> (ng/ml)             | 67    | 53.1    | 52.8     |
| T <sub>max</sub> (hr)                | 0.5   | 0.25    | 0.25     |
| AUC(tf) (ng.hr/ml)                   | 87.6  | 70.1    | 78.1     |
| T <sub>1/2</sub> (hr)                | 1.37  | 1.04    | 1.18     |
| Cl/F (L/hr.kg)                       | 97    | 121     | 109      |
| SCH 34117 in plasma                  |       |         |          |
| C <sub>max</sub> (ng/ml)             | 117   | 65.8    | 89.3     |
| T <sub>max</sub> (hr)                | 3     | 1       | 3        |
| AUC(tf) (ng.hr/ml)                   | 805   | 584     | 705      |
| T <sub>1/2</sub> (hr)                | 6.2   | 4.05    | 6.14     |

**Multiple dose:** Studies were performed in rats, monkeys, mice and rabbits with both SCH 34117 and SCH 29851. Results are summarized below.

Following a 1 week oral gavage administration of SCH 29851 or SCH 34117 (60, 120 and 240 mg/kg) in rats, SCH 34117 was slowly absorbed with a C<sub>max</sub> of 1.5 to 12 hr after SCH 34117 administration (Table 11). Plasma levels increased in a dose-related manner with slow elimination as plasma levels 24 hr post dose were 26-85% of the C<sub>max</sub>. Drug accumulation

increased as the dose increased. Following SCH 29851 administration, systemic exposure to SCH 29851 increased sub-proportionally, was reduced on Day 6 compared to Day 1 and was gender dependent. Maximum plasma levels were noted at 0.5 to 4 hrs after dosing and Day 6 exposure was lower than on day 1. Levels of SCH 34117 peaked at 1-8 hours after dosing and levels increased sub-proportionally with dose. Elimination was again slow and the accumulation ratio increased slightly with dose. Maximum plasma levels with SCH 34117 administration were 1.03 to 4.1 times greater than when SCH 29851 was administered; overall 1.2 to 1.3 times greater on day 0 and 1.5 to 3.2 on day 6.

**Table 11.** Pharmacokinetics in rats following 1-week oral dosing of SCH 34117 or SCH 29851.

| Parameters                                       | 60 mg/kg |         |       |         | 120 mg/kg |         |       |         | 240 mg/kg |         |        |         |
|--|----------|---------|-------|---------|-----------|---------|-------|---------|-----------|---------|--------|---------|
|  | Day 0    |         | Day 6 |         | Day 0     |         | Day 6 |         | Day 0     |         | Day 6  |         |
|  | Males    | Females | Males | Females | Males     | Females | Males | Females | Males     | Females | Males  | Females |
| Administered drug: SCH 34117; Analyte: SCH34117  |          |         |       |         |           |         |       |         |           |         |        |         |
| Cmax (ng/ml)                                     | 864      | 830     | 969   | 1443    | 928       | 1362    | 2060  | 2238    | 1378      | 1512    | 7815   | 6356    |
| Tmax (hr)  | 12       | 6       | 12    | 2       | 6         | 12      | 6     | 8       | 8         | 12      | 1.5    | 8       |
| AUC (0-24) (ng.hr/ml)                            | 14592    | 16970   | 17275 | 27393   | 18982     | 24907   | 44060 | 44969   | 25676     | 29206   | 114828 | 119641  |
| R  | NA       | NA      | 1.18  | 1.61    | NA        | NA      | 2.32  | 1.81    | NA        | NA      | 4.47   | 4.1     |
| Administered drug: SCH 29851; Analyte: SCH 29851 |          |         |       |         |           |         |       |         |           |         |        |         |
| Cmax (ng/ml)                                     | 629      | 1061    | 275   | 579     | 963       | 1350    | 407   | 653     | 1129      | 1614    | 383    | 994     |
| Tmax (hr)  | 1.5      | 0.5     | 1     | 1       | 2         | 0.5     | 1     | 1       | 4         | 1       | 1.5    | 1.5     |
| AUC (0-24) (ng.hr/ml)                            | 3042     | 3051    | 1365  | 2171    | 6372      | 10089   | 2206  | 6139    | 12728     | 21994   | 3985   | 11309   |
| R  | NA       | NA      | 0.45  | 0.71    | NA        | NA      | 0.35  | 0.61    | NA        | NA      | 0.31   | 0.51    |
| Administered drug: SCH 29851; Analyte: SCH 34117 |          |         |       |         |           |         |       |         |           |         |        |         |
| Cmax (ng/ml)                                     | 733      | 1008    | 765   | 986     | 832       | 1130    | 1112  | 1482    | 946       | 1190    | 1679   | 1928    |
| Tmax (hr)  | 4        | 6       | 4     | 8       | 8         | 6       | 2     | 4       | 8         | 6       | 8      | 1       |
| AUC (0-24) (ng.hr/ml)                            | 10826    | 14644   | 11740 | 18655   | 14565     | 20401   | 20340 | 31510   | 19602     | 24670   | 36700  | 37268   |
| R  | NA       | NA      | 1.08  | 1.27    | NA        | NA      | 1.4   | 1.54    | NA        | NA      | 1.87   | 1.51    |

Three week oral gavage dosing with SCH 29851 (72 mg/kg) and SCH 34117 (30 mg/kg) resulted in peak levels of SCH 34117 after SCH 34117 administration within 2-3 hours (Table 12). Similar plasma levels of SCH 34117 were noted after dosing with 30 mg/kg SCH 34117 or 72 mg/kg SCH 29851 and females tended to have greater systemic exposure. 3-OH-SCH 34117 was not detectable in plasma except in a few rats (close to LOQ). Substantial concentrations (up to 58 ng/ml bile at 0-8hr time interval) were found in the bile, indicating conversion in the liver and rapid excretion. The data indicate that the exposure to SCH 34117 following administration to 72 mg/kg SCH 29851 is approximately one-third of that following 30 mg/kg SCH 34117.

**Table 12.** Pharmacokinetics in rats following 3-week oral dosing with SCH 34117 or SCH 29851.

| Parameters                  | Administered:<br>30 mg/kg SCH 34117 |         |          | Administered:<br>72 mg/kg SCH 29851 |         |          | Administered:<br>72 mg/kg SCH 29851 |         |          |
|-----------------------------|-------------------------------------|---------|----------|-------------------------------------|---------|----------|-------------------------------------|---------|----------|
|                             | Analyte: SCH 34117                  |         |          | Analyte: SCH 29851                  |         |          | Analyte: SCH 34117                  |         |          |
|                             | Males                               | Females | Combined | Males                               | Females | Combined | Males                               | Females | Combined |
| C <sub>max</sub><br>(ng/ml) | 953                                 | 1680    | 1270     | 293                                 | 399     | 284      | 1790                                | 2250    | 1890     |
| AUC (0-24)<br>(ng.hr/ml)    | 15500                               | 31800   | 23700    | 1570                                | 1800    | 1690     | 22400                               | 45000   | 33600    |

In monkeys, a 16-day oral gavage administration of SCH 29851 (160 mg/kg) or SCH 34117 (24 mg/kg), resulted in peak levels of SCH 34117 at 8-9 hours post-dosing with SCH 34117 (Table 13). The AUC ratio of SCH 34117 and unconjugated 3-OH-SCH 34117 was similar regardless of which drug administered. Levels of 3-OH-SCH 34117 (conjugated and unconjugated) paralleled that of SCH 34117 indicating rapid conversion and unconjugated 3-OH-SCH 34117 levels were ~ 700 and 390-fold lower than SCH 34117 in males and females, respectively; levels of conjugated 3-OH-SCH 34117 were 29 and 17-fold lower than SCH 34117. Following administration of SCH 29851, peak drug concentration was noted at 5-7 hours. Increases were paralleled by SCH 34117 and 3-OH-SCH 34117. Levels of unconjugated 3-OH-SCH 34117 were again 580 to 340-fold lower than SCH 34117 in males and females, respectively. Levels of unconjugated 3-OH-SH 34117 were ~ 25-fold lower than those of conjugated metabolite.

**Table 13.** Pharmacokinetics in monkeys after 16-day oral dosing of SCH 34117 or SCH 29851.

|                           | C <sub>max</sub> (ng/ml)         |         |          | AUC(0-24) (ng.hr/ml) |         |          |
|---------------------------|----------------------------------|---------|----------|----------------------|---------|----------|
|                           | Males                            | Females | Combined | Males                | Females | Combined |
| Analyte                   | Administered SCH 34117 24 mg/kg  |         |          |                      |         |          |
| SCH 34117                 | 1630                             | 992     | 1311     | 33185                | 16484   | 24835    |
| 3-OH-SCH 34117            | 2.51                             | 2.81    | 2.66     | 47.3                 | 42.7    | 45       |
| Conjugated 3-OH-SCH 34117 | 77.4                             | 86.5    | 81.9     | 1142                 | 953     | 1048     |
| Total 3-OH-SCH 34117      | 79.7                             | 89.3    | 84.5     | 1189                 | 996     | 1093     |
|                           | Administered SCH 29851 160 mg/kg |         |          |                      |         |          |
| SCH 29851                 | 70.1                             | 72.7    | 71.2     | 734                  | 1012    | 853      |
| SCH 34117                 | 1705                             | 1450    | 1596     | 35160                | 28969   | 32506    |
| 3-OH-SCH 34117            | 2.91                             | 3.94    | 3.35     | 60.9                 | 84.9    | 71.2     |
| Conjugated 3-OH-SCH 34117 | 81                               | 112     | 94.2     | 1549                 | 2233    | 1842     |
| Total 3-OH-SCH 34117      | 83.6                             | 115     | 97.1     | 1610                 | 2318    | 1914     |

In female New Zealand white rabbits, a two week oral administration of SCH 29851 (48 mg/kg) or SCH 34117 (30 mg/kg) resulted in a 3-OH-SCH 34117 exposure that was 370-fold lower than SCH 34117 in plasma following administration of SCH 34117 (Table 14). Following administration of SCH 29851, rapid absorption and conversion was observed. The rabbit is the only species tested in which systemic exposure to SCH 34117 was less than SCH 29851 following administration of SCH 29851; the systemic exposures to SCH 34117 and 3-OH-SCH 34117 were 2.4-fold and 823-fold lower than SCH 29851 after administration of SCH 29851. The extent of conversion of SCH 34117 to 3-OH-SCH 34117 was comparable after administration of either SCH 29851 or SCH 34117. This uniqueness of rabbit metabolism suggests that a teratology study should be performed with SCH 34117.

**Table 14.** Pharmacokinetics in rabbits following 2-week oral dosing with SCH 34117 or SCH 29851.

| Parameters                  | Administered:<br>30 mg/kg SCH 34117 |                            | Administered:<br>48 mg/kg SCH 29851 |                       |                            |
|-----------------------------|-------------------------------------|----------------------------|-------------------------------------|-----------------------|----------------------------|
|                             | Analyte:<br>SCH 34117               | Analyte:<br>3-OH-SCH 34117 | Analyte:<br>SCH 29851               | Analyte:<br>SCH 34117 | Analyte:<br>3-OH-SCH 34117 |
| C <sub>max</sub><br>(ng/ml) | 459                                 | 1.43                       | 855                                 | 169                   | 0.605                      |
| T <sub>max</sub> (hr)       | 2.5                                 | 2.5                        | 1                                   | 3.2                   | 2.7                        |
| AUC (0-24)<br>(ng.hr/ml)    | 3081                                | 8.35                       | 2791                                | 1159                  | 3.39                       |

In studies to assess exposure to 3-OH-SCH 34117 at the highest doses tested in previous carcinogenicity studies with loratadine, Crl:CD (SD)BR rats and Crl:CD-1 mice were administered SCH 29851 (25 and 40 mg/kg/day, respectively) for 3 weeks in a drug/diet mixture. The results were similar to previous TK studies with loratadine (Table 15). In rats, exposure to SCH 34117 was several fold (19-35) higher than SCH 29851. 3-OH-SCH 34117 was not quantifiable in plasma but it was found in bile (substantial levels 8.41-41.3 ng/ml bile; 0 to 24 hours after dosing). In mice, exposure to SCH 34117 was also several fold higher than SCH 29851. In addition, 3-OH-SCH 34117 was quantifiable in both plasma and bile but were 20- to 1000-fold lower than the levels of the other two analytes in plasma while bile concentrations were higher (37.4-156 ng/ml bile; 0 to 16 hours after dosing). The data demonstrate that rat and mouse livers are capable of generating 3-OH-SCH 34117, but it is rapidly excreted via bile.

**Table 15.** Pharmacokinetics in mice and rats following 3-week drug/diet mixture with SCH 29851.

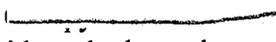
| Analyte         | C <sub>max</sub> (ng/ml) |         |          | AUC(0-24) (ng.hr/ml) |         |          |
|-----------------|--------------------------|---------|----------|----------------------|---------|----------|
|                 | Males                    | Females | Combined | Males                | Females | Combined |
| Rats (25 mg/kg) |                          |         |          |                      |         |          |
| SCH 29851       | 30.6                     | 26.1    | 28.4     | 458                  | 425     | 442      |
| SCH 34117       | 492                      | 716     | 587      | 8820                 | 15100   | 12000    |
| 3-OH-SCH 34117  | NQ                       | NQ      | NQ       | NQ                   | NQ      | NQ       |
| Mice (40 mg/kg) |                          |         |          |                      |         |          |
| SCH 29851       | 2.47                     | 2.18    | 2.29     | 45.5                 | 40.8    | 43.1     |
| SCH 34117       | 146                      | 72.5    | 109      | 2140                 | 1480    | 1810     |
| 3-OH-SCH 34117  | 0.211                    | 0.0836  | 0.129    | 1.94                 | 1.34    | 1.64     |

**Protein binding:** SCH 34117 (5-400 ng/ml) was moderately bound to plasma proteins in mice, rats, monkeys or humans (Table 16). Rodent species displayed higher binding than humans or monkeys. There appeared to be a slight concentration dependent binding in the plasma in all species. Mean serum protein binding was not affected by heparin, however, mean serum binding was higher in monkeys than plasma protein binding.

**Table 16.** Comparative protein binding of SCH 34117.

| Species | % <sup>14</sup> C-SCH 34117 Bound |     |
|---------|-----------------------------------|-----|
|         | Mean                              | %CV |
| Mouse   | 94.4                              | 1.8 |
| Rat     | 90.5                              | 2.4 |
| Monkey  | 85.8                              | 1.3 |
| Human   | 85.6                              | 1.9 |

**Metabolism:** Metabolism studies were performed using oral doses of SCH 34117 and SCH 29851 in rats, monkeys and mice. The results are summarized below.

In rats, a single dose of SCH 34117 (6.5 mg/kg) was extensively metabolized via mono- or dihydroxylation at primarily the 5- and/or 6- positions although high levels of unchanged SCH 34117 were observed (Table 17). Male rats achieved high circulating levels of SCH 357130, a heretofore unknown  derivative. Minor metabolites included SCH 45581, SCH 45581-glucuronide and other unknown compounds. Profiles from urine, bile and feces were similar. No SCH 34117 specific metabolites were noted compared to loratadine (Table 18).

**Table 17.** Metabolism of SCH 34117 in rats following a single oral dose.

|                         | Radioactivity     |    |    |               |                 |                 |             |                 |                 |           |                 |                 |
|-------------------------|-------------------|----|----|---------------|-----------------|-----------------|-------------|-----------------|-----------------|-----------|-----------------|-----------------|
|                         | % of chromatogram |    |    |               |                 |                 |             |                 |                 | % of dose |                 |                 |
|                         | Male plasma       |    |    | Female plasma |                 |                 | Bile (4 hr) |                 | Urine (0-48 hr) |           | Feces (0-48 hr) |                 |
| Major metabolites       | 1 <sup>a</sup>    | 4  | 12 | 1             | 4               | 12              | M           | F               | M               | F         | M               | F               |
| SCH 34117               | 34                | 18 | 6  | 75            | 66              | 53              | 3           | 5               | <1              | 2         | 13              | 15              |
| SCH 39090 <sup>c</sup>  | 9                 | 6  | 1  | 8             | 11              | 9               | 12          | 37              | 8               | 12        | 12              | 21              |
| SCH 39091 <sup>d</sup>  | 5                 | 5  | 2  | 5             | 7               | 9               | 12          | 25              | 5               | 8         | 12              | 16              |
| SCH 218985 <sup>e</sup> | <1                | 6  | 3  | <1            | <1              | <1              | 27          | 15              | 7               | 4         | 7               | 5               |
| SCH 357130 <sup>f</sup> | 38                | 49 | 62 | 3             | 5               | 8               | <1          | <1              | <1              | <1        | -- <sup>b</sup> | -- <sup>b</sup> |
| SCH 356467 <sup>g</sup> | 4                 | 3  | 4  | 2             | <1              | 5               | <1          | <1              | <1              | <1        | 2               | <1              |
| Unknown C1-C6           | 5                 | 10 | 13 | <1            | -- <sup>b</sup> | -- <sup>b</sup> | <1          | -- <sup>b</sup> | 5               | <1        | -- <sup>b</sup> | -- <sup>b</sup> |

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5-OH-SCH 34117

e: 5,6-dihydroxy-SCH 34117

f: Metabolite B: 8-chloro-6,11-dihydro-11-(4-pyridinyl-5H-[5,6]cyclohepta[1,2-b]pyridine-N-oxide

g: Metabolite E: 8-chloro-6,11-dihydro-11-(4-pyridinyl-5H-[5,6]cyclohepta[1,2-b]pyridine

A similar profile was observed following administration of 8 mg/kg SCH 29851, as metabolism was again primarily via mono or dihydroxylation at 5- or 6- positions and descarboethoxylation with minor amounts of SCH 45581, SCH 45581-glucuronide and several unknown components (Table 18). Male rats again achieved high circulating levels of SCH 357130.

**Table 18.** Metabolism of SCH 29851 in rats following a single oral dose.

|                         | Radioactivity     |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
|-------------------------|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                         | % of chromatogram |                 |                 |                 |                 |                 | % of dose       |                 |                 |                 |                 |                 |
|                         | Male plasma       |                 |                 | Female plasma   |                 |                 | Bile (24 hr)    |                 | Urine (0-48 hr) |                 | Feces (0-48 hr) |                 |
| Major metabolites       | 1 <sup>a</sup>    | 6               | 12              | 1               | 6               | 12              | M               | F               | M               | F               | M               | F               |
| SCH 29851               | 17                | 6               | <1              | 16              | 3               | 3               | <1              | <1              | -- <sup>b</sup> | -- <sup>b</sup> | 2               | 2               |
| SCH 34117               | 13                | 16              | 9               | 33              | 37              | 31              | 4               | 2               | 1               | 2               | 8               | 10              |
| SCH 39090 <sup>c</sup>  | 8                 | 10              | 11              | 5               | 10              | 14              | 6               | 21              | 7               | 10              | 14              | 18              |
| SCH 39091 <sup>d</sup>  | 5                 | 9               | 8               | 3               | 10              | 4               | 8               | 23              | 8               | 8               | 17              | 23              |
| SCH 218985 <sup>e</sup> | 4                 | 7               | 14              | <1              | <1              | <1              | 18              | 19              | 7               | 4               | 7               | 5               |
| SCH 357130 <sup>f</sup> | 21                | 29              | 48              | 4               | 14              | 17              | <1              | <1              | <1              | <1              | -- <sup>b</sup> | -- <sup>b</sup> |
| SCH 356467 <sup>g</sup> | 2                 | 5               | 5               | 2               | 2               | 9               | <1              | <1              | -- <sup>b</sup> | -- <sup>b</sup> | 2               | <1              |
| Unknown C1-C6           | 4                 | 6               | 1               | 2               | 3               | 7               | -- <sup>b</sup> | -- <sup>b</sup> | <1              | <1              | -- <sup>b</sup> | <1              |
| Metabolite H            | -- <sup>b</sup>   | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | 3               | 3               | -- <sup>b</sup> | -- <sup>b</sup> | 2               | 3               |
| Unknowns I1-I2          | -- <sup>b</sup>   | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | 16              | 16              | -- <sup>b</sup> | -- <sup>b</sup> | 5               | 4               |

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5-OH-SCH 34117

e: 5,6-dihydroxy-SCH 34117

f: Metabolite B: 8-chloro-6,11-dihydro-11-(4-pyridinyl-5H-[5,6]cyclohepta[1,2-b]pyridine-N-oxide

g: Metabolite E: 8-chloro-6,11-dihydro-11-(4-pyridinyl-5H-[5,6]cyclohepta[1,2-b]pyridine

In monkeys SCH 34117 (6.5 mg/kg) metabolism included mono- and dihydroxylation, glucuronidation and possible N-oxidation (Table 19). Further characterization of SCH 34117-Glu suggest the metabolite is formed through N-oxidation of pyridine nitrogen and subsequent glucuronidation. Minor to trace levels of SCH 45581 (3-OH-SCH 34117) and SCH 45581-glucuronide and several unknowns were detected. No SCH 34117 specific metabolites were noted compared to loratadine (Table 20).

**Table 19.** Metabolism of SCH 34117 in monkeys following a single oral dose.

|                        | Radioactivity     |    |               |    |                |    |                 |    |                 |                 |
|------------------------|-------------------|----|---------------|----|----------------|----|-----------------|----|-----------------|-----------------|
|                        | % of chromatogram |    |               |    |                |    | % of dose       |    |                 |                 |
|                        | Male plasma       |    | Female plasma |    | Bile (0-48 hr) |    | Urine (0-48 hr) |    | Feces (0-48 hr) |                 |
| Major metabolites      | 4 <sup>a</sup>    | 12 | 4             | 12 | M              | F  | M               | F  | M               | F               |
| SCH 34117              | 25                | 22 | 23            | 9  | 7              | 6  | <1              | <1 | 2               | 5               |
| SCH 39090 <sup>c</sup> | 7                 | 8  | 10            | 5  | 9              | 13 | 4               | 3  | 10              | 19              |
| SCH 39091 <sup>d</sup> | 4                 | 3  | 4             | 5  | 14             | 23 | 2               | 2  | 12              | 19              |
| SCH 39090-Glu          | 8                 | 7  | 10            | 4  | 4              | <1 | 3               | 4  | -- <sup>b</sup> | -- <sup>b</sup> |
| SCH 39091-Glu          | 17                | 19 | 28            | 13 | 7              | 4  | 6               | 6  | -- <sup>b</sup> | -- <sup>b</sup> |
| Monooxy-SCH 34117-Glu  | 3                 | 2  | 9             | 36 | 29             | 38 | 1               | <1 | -- <sup>b</sup> | -- <sup>b</sup> |
| OH-SCH 34117-Glu       | 21                | 20 | 3             | <1 | 11             | 2  | 2               | 3  | -- <sup>b</sup> | -- <sup>b</sup> |
| di-OH-SCH 34117-Glu    | 3                 | 3  | <1            | 7  | 7              | 7  | <1              | <1 | -- <sup>b</sup> | -- <sup>b</sup> |

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5-OH-SCH 34117

A similar profile was observed following administration of 8 mg/kg SCH 29851, as only minor levels of SCH 29851 were detected and metabolism was again primarily via descarboethoxylation, mono- or dihydroxylation at 5- or 6- positions, glucuronidation and possibly N-oxidation and with minor amounts of SCH 45581, SCH 45581-glucuronide and several unknown components (Table 20).

**Table 20.** Metabolism of SCH 29851 in monkeys following a single oral dose.

|                          | Radioactivity     |    |               |    |                   |    |                    |                 |                    |                 |
|--------------------------|-------------------|----|---------------|----|-------------------|----|--------------------|-----------------|--------------------|-----------------|
|                          | % of chromatogram |    |               |    |                   |    | % of dose          |                 |                    |                 |
|                          | Male plasma       |    | Female plasma |    | Bile<br>(0-48 hr) |    | Urine<br>(0-48 hr) |                 | Feces<br>(0-96 hr) |                 |
| <b>Major metabolites</b> | 4 <sup>a</sup>    | 12 | 4             | 12 | M                 | F  | M                  | F               | M                  | F               |
| SCH 29851                | 2                 | <1 | 4             | <1 | <1                | <1 | -- <sup>b</sup>    | -- <sup>b</sup> | 11                 | 1               |
| SCH 34117                | 2                 | 3  | 8             | 3  | 2                 | 3  | <1                 | <1              | 2                  | 2               |
| SCH 39090 <sup>c</sup>   | 1                 | 3  | 3             | <1 | 12                | 13 | 3                  | 4               | 12                 | 14              |
| SCH 39091 <sup>d</sup>   | 4                 | 2  | 12            | <1 | 32                | 53 | 3                  | 3               | 20                 | 28              |
| SCH 39090-Glu            | 7                 | 4  | 6             | 4  | 3                 | <1 | 3                  | 5               | -- <sup>b</sup>    | -- <sup>b</sup> |
| SCH 39091-Glu            | 17                | 13 | <1            | 12 | 2                 | 3  | 12                 | 13              | -- <sup>b</sup>    | -- <sup>b</sup> |
| Monoxy-SCH<br>34117-Glu  | 2                 | 4  | 30            | 20 | 7                 | 15 | <1                 | <1              | -- <sup>b</sup>    | -- <sup>b</sup> |
| OH-SCH 34117-<br>Glu     | 4                 | 5  | <1            | 5  | <1                | 2  | 2                  | 2               | -- <sup>b</sup>    | -- <sup>b</sup> |
| di-OH-SCH 34117-<br>Glu  | 3                 | 5  | 1             | 3  | 1                 | 1  | <1                 | <1              | -- <sup>b</sup>    | -- <sup>b</sup> |
| 3-OH-SCH 29851-<br>Glu   | 13                | 17 | 2             | 8  | 3                 | <1 | <1                 | <1              | -- <sup>b</sup>    | -- <sup>b</sup> |
| OH-SCH 29851-<br>Glu     | 12                | 25 | 10            | 25 | 16                | 1  | 1                  | <1              | -- <sup>b</sup>    | -- <sup>b</sup> |
| di-OH-SCH 29851-<br>Glu  | 3                 | <1 | 3             | 5  | 3                 | <1 | <1                 | <1              | -- <sup>b</sup>    | -- <sup>b</sup> |
| Unknowns K1-K3           | 6                 | <1 | 10            | <1 | <1                | <1 | <1                 | <1              | 4                  | 8               |
| Unknown-K-Glu            | 2                 | 2  | 3             | 1  | 9                 | 6  | 2                  | 2               | -- <sup>b</sup>    | -- <sup>b</sup> |

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5- OH-SCH 34117

In the CD-1 Mouse, significant levels of SCH 34117 remained, while the main route of metabolism was hydroxylation at the 5- or 6- positions following a single dose of 6.5 mg/kg (Table 21). Minor metabolites included SCH 45581 and SCH 45581-glucuronide. No SCH 34117 specific metabolites were noted compared to loratadine (Table 22).

**Table 21.** Metabolism of SCH 34117 in mice following a single oral dose.

|                        | Radioactivity     |    |    |               |    |     |                 |                 |                 |                 |                 |                 |
|------------------------|-------------------|----|----|---------------|----|-----|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                        | % of chromatogram |    |    |               |    |     |                 |                 |                 | % of dose       |                 |                 |
|                        | Male plasma       |    |    | Female plasma |    |     | Bile (4 hr)     |                 | Urine (0-48 hr) |                 | Feces (0-48 hr) |                 |
| Major metabolites      | 1 <sup>a</sup>    | 4  | 12 | 1             | 4  | 12  | M               | F               | M               | F               | M               | F               |
| SCH 34117              | 41                | 38 | 65 | 39            | 32 | 100 | 45              | 30              | 5               | 2               | 13              | 11              |
| SCH 39090 <sup>c</sup> | 3                 | 4  | <1 | 2             | 5  | <1  | 2               | 10              | 7               | 7               | 9               | 8               |
| SCH 39091 <sup>d</sup> | 5                 | 13 | 14 | 7             | 8  | <1  | 19              | 40              | 24              | 22              | 17              | 19              |
| Unknown D <sup>e</sup> | 15                | 13 | 7  | 20            | 14 | <1  | -- <sup>b</sup> |

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5- OH-SCH 34117

e: covalent adduct (N-formyl derivative)

After dosing with 8 mg/kg SCH 29851, metabolism was primarily through hydroxylation, decarboethoxylation and glucuronidation (Table 22). 3-OH-SCH 29851-glucuronide was the major circulating metabolite and persisted for at least 12 hours. Minor metabolites included SCH 45581 and SCH 45581-glucuronide and others of unknown structure.

**Table 22.** Metabolism of SCH 29851 in mice following a single oral dose.

|                          | Radioactivity     |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
|--------------------------|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                          | % of chromatogram |                 |                 |                 |                 |                 |                 |                 |                 | % of dose       |                 |                 |
|                          | Male plasma       |                 |                 | Female plasma   |                 |                 | Bile (4 hr)     |                 | Urine (0-48 hr) |                 | Feces (0-48 hr) |                 |
| Major metabolites        | 1 <sup>a</sup>    | 4               | 12              | 1               | 4               | 12              | M               | F               | M               | F               | M               | F               |
| SCH 29851                | 4                 | 2               | -- <sup>b</sup> | 6               | 1               | -- <sup>b</sup> | 3               | 3               |
| SCH 34117                | 15                | 13              | 6               | 9               | 7               | 7               | 3               | 3               | 2               | <1              | 5               | 3               |
| SCH 39090 <sup>c</sup>   | 6                 | 2               | -- <sup>b</sup> | <1              | <1              | -- <sup>b</sup> | 1               | 2               | 4               | 7               | 8               | 9               |
| SCH 39091 <sup>d</sup>   | 17                | 10              | -- <sup>b</sup> | 1               | 2               | -- <sup>b</sup> | 3               | 8               | 11              | 14              | 16              | 15              |
| 5- or 6-OH-SCH 29851     | 16                | 9               | 8               | 22              | 7               | <1              | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | 5               | 2               |
| 5- or 6-OH-SCH 29851-Glu | -- <sup>b</sup>   | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | 9               | 10              | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> |
| 3-OH-SCH 29851           | <1                | <1              | -- <sup>b</sup> | 2               | 3               | -- <sup>b</sup> | 2               | 3               | -- <sup>b</sup> | -- <sup>b</sup> | 7               | 17              |
| 3-OH-SCH 29851-Glu       | 23                | 35              | 75              | 30              | 46              | 93              | 22              | 22              | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> |
| di-OH-SCH 29851-Glu      | 1                 | -- <sup>b</sup> | -- <sup>b</sup> | 3               | -- <sup>b</sup> | -- <sup>b</sup> | 42              | 36              | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> | -- <sup>b</sup> |

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5- OH-SCH 34117

**In vitro studies:** In vitro metabolism of <sup>14</sup>C-SCH 29851 (0.26 μM) and <sup>14</sup>C-SCH 34117 (0.32 μM) was investigated following incubation of drugs with rat, mouse, rabbit, cynomolgus monkey and human hepatocytes and microsomes (Table 23). SCH 39090 (5-OH-SCH 34117) and 39091 (6-OH-SCH 34117) were the major metabolites in rat, mouse, rabbit, monkey hepatocytes and microsomes. In humans, unchanged SCH 34117 was primarily detected with much smaller levels of SCH 45581 (3-OH-SCH 34117), SCH 39090 and 39091. No SCH 34117 specific metabolites were observed and all in vitro metabolites had been detected in vivo experiments.

The in vitro studies reflect the types of metabolites and the general species differences in terms of metabolite production, although specific proportions differ.

**Table 23.** In vitro metabolism of SCH 34117 and SCH 29851.

| Species | Hepatocytes   |  | Microsomes   |  |
|---------|---|--|--|--|
|         | SCH 34117   | SCH 29851  | SCH 34117  | SCH 29851  |
| Rat     | SCH 34117 (2%)<br>SCH 39090 (7%)<br>SCH 39091 (8%)<br>OH-SCH 34117-glucuronide (7%)<br>SCH 218985 (66%)                       | SCH 29851 (5%)<br>SCH 34117 (2%)<br>SCH 39090 (5%)<br>SCH 39091 (8%)<br>OH-SCH 34117-glucuronide (12%)<br>SCH 218985 (52%)                     | SCH 34117 (2%)<br>SCH 39090 (22%)<br>SCH 39091 (19%)<br>SCH 357130 (10%)<br>SCH 218985 (25%) | SCH 29851 (4%)<br>SCH 34117 (7%)<br>SCH 39090 (19%)<br>SCH 39091 (20%)<br>SCH 357130 (6%)<br>SCH 218985 (19%)<br>Unknowns (19%)  |
| Mouse   | SCH 34117 (32%)<br>SCH 39090 (11%)<br>SCH 39091 (38%)   | SCH 29851 (7%)<br>SCH 34117 (2%)<br>SCH 39090 (13%)<br>SCH 39091 (44%)<br>OH-SCH 29851-glucuronide (14%)                                       | SCH 34117 (79%)<br>SCH 39090 (4%)<br>SCH 39091 (11%)<br>Unknown D (4%)                       | SCH 29851 (15%)<br>SCH 34117 (12%)<br>SCH 39090 (9%)<br>SCH 39091 (11%)<br><br>3-OH-SCH 29851 (<1%)<br>5-OH-SCH 29851 (<5%)<br>6-OH-SCH 29851 (<8%)<br>dihydroxy-SCH 29851 (16%)<br>Unknowns (18%) |
| Rabbit  | SCH 34117 (2%)<br>SCH 39090 (18%)<br>SCH 39091 (58%)  | SCH 29851 (10%)<br>SCH 34117 (<1%)<br>SCH 39090 (11%)<br>SCH 39091 (53%)<br>3-OH-SCH 34117-glucuronide (8%)                                    | SCH 34117 (<1%)<br>SCH 39090 (44%)<br>SCH 39091 (44%)<br>SCH 45581 (<1%)                     | SCH 34117 (<1%)<br>SCH 39090 (35%)<br>SCH 39091 (58%)<br>SCH 45581 (<1%)   |
| Monkey  | SCH 34117 (8%)<br>SCH 39090 (37%)<br>SCH 39091 (16%)<br>OH-SCH 34117-glucuronide (21%)<br>Monooxy-SCH 34117-glucuronide (11%) | SCH 29851 (5%)<br>SCH 34117 (3%)<br>SCH 39090 (17%)<br>SCH 39091 (13%)<br>OH-SCH 34117-glucuronide (39%)<br>Monooxy-SCH 34117-glucuronide (6%) | SCH 34117 (51%)<br>SCH 39090 (25%)<br>SCH 39091 (23%)  | SCH 29851 (<1%)<br>SCH 34117 (38%)<br>SCH 39090 (19%)<br>SCH 39091 (43%)   |
| Human   | SCH 34117 (97%)<br>SCH 39090 (<1%)<br>SCH 39091 (<1%)<br>SCH 45581 (3%)   | SCH 29851 (7%)<br>SCH 34117 (75%)<br>SCH 39090 (5%)<br>SCH 39091 (9%)<br>SCH 45581 (3%)  | SCH 34117 (96%)<br>Unknown D (4%)  | SCH 29851 (19%)<br>SCH 34117 (80%)   |

Due to extensive 3-hydroxylation of SCH 34117 in humans, a study was conducted to ascertain if it could be generated by rodent livers via in vitro incubation of SCH 34117 and SCH 29851 (0.3 to 250  $\mu\text{M}$ ) in rat and mouse liver microsomes and S9 fractions from normal and aroclor-treated animals. SCH 29851 was converted to SCH 34117 in both species and both drugs yielded SCH 39090 and 39091. At a low substrate concentration (0.3  $\mu\text{M}$ ), 3-hydroxy SCH 34117 (SCH

45581) was not detected in any preparation. However, at 35  $\mu$ M significant levels of 3-OH SCH 29851 (2-7%) formed from SCH 29851 and trace levels of 3-OH-SCH 34117 (<1%) formed from SCH 29851 and SCH 34117 were produced. Incubation at 35  $\mu$ M was optimal for 3-OH-SCH 34117. SCH 29851 specific metabolites included monohydroxy SCH 29851 as well as mono-keto SCH 29851. No SCH 34117 specific metabolites were noted in liver preparations. Upon incubation of liver microsomes or S9 fractions from normal or Aroclor treated rats and mice, both loratadine and SCH 34117 generated similar levels of 3-OH-SCH 34117.

**Excretion:** Comparative elimination of SCH 34117 or SCH 29851-related radioactivity is summarized in Table 24. Elimination was primarily via the feces in all species with the biliary route playing a significant role.

**Table 24.** Elimination of SCH 34117- and SCH 29851-related radioactivity

| Species | Dose                                   | Feces  | Urine  | Other | Total recovery |
|---------|--|--------|--------|-------|----------------|
| Mouse   | Single, 6.5 mg/kg SCH 34117 , po       | 45     | 37     | 3     | 83.6-86.3      |
| Mouse   | Single, 8 mg/kg SCH 29851 , po         | 60     | 20     | < 2   | 80.6-82.6      |
| Rats    | Single 6.5 mg/kg, po or IV             | 65     | 28     | 1     | 94.6-97.2%     |
| Rats    | Single oral 8 mg/kg SCH 9851           | 68     | 27     | <1    | 95-96.9%       |
| Monkeys | Single oral or IV, 6.5 mg/kg SCH 34117 | 41-51% | 25-31% | 7-12% | 80.1-87.1%     |
| Monkeys | Single oral or IV, 8 mg/kg SCH 29851   | 58%    | 29%    | 7-10% | 96%            |

**Summary of Pharmacokinetics:** Single dose pharmacokinetic studies demonstrated that SCH 34117 (6.5 mg/kg, oral) was well absorbed (45-94% in rats, 51% in monkeys). Systemic exposures were similar between rats and monkeys but greater in the mouse. While no gender differences were noted in the mouse or monkey, females rats exhibited greater systemic exposure than males. Following oral administration of 8 mg/kg SCH 29851, systemic exposure to SCH 34117 was 8-20-fold greater in rats and 8-11-fold greater in mice and monkeys. With repeat dosing, exposures were greater in female rats than in males following 3-week oral dosing with 30 mg/kg although the gender-related difference was not as obvious with 1 week dosing at 60-240 mg/kg. Drug accumulation was evident with continued dosing and systemic exposure to SCH 34117 was 14-25-fold greater than SCH 29851 exposure following administration of SCH 29851. In a 16-day oral monkey study, males demonstrated a 2-fold increase in systemic exposure than females. The metabolite 3-OH-SCH 34117 (conjugated and unconjugated) was also detected at 17-29-fold (conjugated) and 390-700-fold (unconjugated) below SCH 34117. Following SCH 29851 administration, exposure to SCH 34117 was 38-fold greater than that of the parent drug. In rabbits, 3-OH-SCH 34117 was detected at levels 370 times below that of SCH 34117 following 2-week oral administration of SCH 34117. In addition, the rabbit is the only species tested in which systemic exposure to SCH 34117 is less than SCH 29851 (2.4-fold) following SCH 29851 administration. Results of a drug/diet administration to mice and rats were similar to previous toxicokinetic studies. The metabolite 3-OH-SCH 34117 was undetected in rat plasma and only at low levels in mouse plasma. However, significant levels were noted in the bile suggesting conversion of SCH 34117 and rapid excretion. Metabolism of SCH 34117 was extensive (greater than 95%) and occurred through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Minor

to trace levels of SCH 45581 (3-OH-SCH 34117) and SCH 45581-glucuronide and several unknowns were also detected. 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. Compared to the metabolism profile of loratadine, no SCH 34117-specific metabolites were observed. Excretion of SCH 34117 was primarily via the feces (41-68%) in mice, rats and monkeys with biliary excretion playing a significant role.

### TOXICOLOGY:

Toxicology studies with SCH 34117 were submitted and previously reviewed under IND 55,364. Studies have been conducted in rats, monkeys and mice. The duration of dosing ranged from single dose to 3 months in rats and monkeys. Acute toxicity has been evaluated by oral and intraperitoneal routes of administration and repeat dose studies have been conducted using the oral route of administration. The sponsor sought agreement with the Division concerning a bridging strategy for the toxicology program from the loratadine program to SCH 34117. Following evaluation of the 3-month toxicity studies with SCH 34117, the Division agreed that both compounds produced comparable toxicity profiles and that the sponsor need not perform chronic toxicity studies with SCH 34117. These studies are fully discussed in the Overall Summary and Evaluation.

### GENETIC TOXICOLOGY:

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. The sponsor also submitted two assays (a bacterial reverse mutation assay and an *in vitro* chromosome aberration assay using human lymphocytes) to the NDA as part of their effort to qualify the presence of two synthesis impurities. These studies, which are reviewed below, also produced negative results.

Bacterial mutagenicity study (Ames Assay) of SCH 34117 with impurities and degradants

*Study No.:* 99287      *Volume:* 10.8

*Study endpoint:* Mutagenicity  
*Study Dates:* Starting date July 19, 1999; report issued March 10, 2000  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch 99-34117-X-202) diluted in DMSO  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Methods:** SCH 34117 (polymorph ratio: Form I (9%) and Form II (91%)), with added synthesis impurities \_\_\_\_\_ and degradants \_\_\_\_\_, was assayed in 5 *Salmonella* tester strains and 1 *E. coli* strains ± metabolic activation by Aroclor 1254-induced rat liver S9 fraction. This study was performed as part of the sponsor's qualification for proposed specifications for the synthesis impurities. The following strains and positive controls were used in 3 plate incorporation reverse mutation tests:

| Strain   | Positive Controls Without S9 (µg/plate) | Positive Controls With S9 (µg/plate) |
|----------|---|--------------------------------------|
| TA 1535  | sodium azide (5)                        | 2-aminoanthracene (2.5)              |
| TA 97a   | 9-aminoacridine (75)                    | 2-aminoanthracene (2.5)              |
| TA 98    | 2-Nitrofluorene (5)                     | 2-aminoanthracene (2.5)              |
| TA 100   | sodium azide (5)                        | 2-aminoanthracene (2.5)              |
| TA 102   | Cumene hydroperoxide (200)              | 2-aminoanthracene (5)                |
| WP2 uvrA | N-Ethyl-N'-nitro-N-nitrosoguanidine (2) | 2-aminoanthracene (20)               |

SCH 34117 and positive controls were dissolved in DMSO. Three dosing trials were performed to achieve valid and reproducible results: dose selection for the first trial was based upon results of a previous bacterial mutagenicity trial with SCH 34117 (see IND 55,364 Original Review), selection for second trial was based upon results from the first, and selection for trial 3 was based upon results of the second. Dose selection was based upon cytotoxicity (a reduction in revertant colony counts by ~ 30% below solvent control, inhibition of background bacterial lawn growth and "additional factors based on scientific judgment").

| Bacterial strain | Phase         | Trial 1 - Doses (µg/plate)    | Trial 2 - Doses (µg/plate)    | Trial 3 - Doses (µg/plate)    |
|------------------|---------------|-------------------------------|-------------------------------|-------------------------------|
| TA 1535          | nonactivation | 46.9, 93.8, 187.5, 375, 750   | 46.9, 93.8, 187.5, 375, 750   | Not tested                    |
| TA 97a           | nonactivation | 5.9, 11.7, 23.4, 46.9, 93.8   | 46.9, 93.8, 187.5, 375, 750   | Not tested                    |
| TA 98            | nonactivation | 46.9, 93.8, 187.5, 375, 750   | 46.9, 93.8, 187.5, 375, 750   | Not tested                    |
| TA 100           | nonactivation | 23.4, 46.9, 93.8, 187.5, 375  | 23.4, 46.9, 93.8, 187.5, 375  | Not tested                    |
| TA 102           | nonactivation | 11.7, 23.4, 46.9, 93.8, 187.5 | 11.7, 23.4, 46.9, 93.8, 187.5 | 11.7, 23.4, 46.9, 93.8, 187.5 |
| WP2uvrA          | nonactivation | 94, 188, 375, 750, 1500       | 94, 188, 375, 750, 1500       | Not tested                    |
| TA 1535          | activation    | 93.8, 187.5, 375, 750, 1500   | 94, 188, 375, 750, 1500       | Not tested                    |
| TA 97A           | activation    | 5.9, 11.7, 23.4, 46.9, 93.8   | 46.9, 93.8, 187.5, 375, 750   | Not tested                    |
| TA 98            | activation    | 46.9, 93.8, 187.5, 375, 750   | 46.9, 93.8, 187.5, 375, 750   | Not tested                    |
| TA 100           | activation    | 23.4, 46.9, 93.8, 187.5, 375  | 94, 188, 375, 750, 1500       | 46.9, 93.8, 187.5, 375, 750   |
| TA 102           | activation    | 11.7, 23.4, 46.9, 93.8, 187.5 | 11.7, 23.4, 46.9, 93.8, 187.5 | Not tested                    |
| WP2uvrA          | activation    | 94, 188, 375, 750, 1500       | 94, 188, 375, 750, 1500       | 11.7, 23.4, 46.9, 93.8, 187.5 |

The experiments were performed using triplicate plates at each concentration incubated for 40-56 hours ± S9. Tests were valid if overnight bacterial cultures reached a density of at least  $5 \times 10^8$  cells/ml for bacterial strains and  $\sim 15 \times 10^8$  cells/ml for *E. coli*, the mean number of revertant colonies/plate in the solvent control was within the range of the historical solvent control values of the same strain and the mean number of induced revertants/plate in the positive controls was at least three-fold greater than the mean of its concurrent solvent control for TA 1535, and at least two-fold greater than the mean of their respective concurrent controls for *E. coli* and other *Salmonella* strains. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in at least one of the six tester strains, the magnitude of increase was at least two-fold above the solvent control for strains TA 97A, TA

98, TA 100, TA 102 and WP2uvrA, and three-fold above the solvent control for strain TA 1535. In addition, a dose-response increase of revertant counts in treated plates above that of the solvent control was observed in at least two dose levels, and the increases were reproducible in independent trials.

**Results:** SCH 34117 with added impurities and degradants did not increase revertant colony counts,  $\pm$  S9 activation in any of the strains tested. Positive controls significantly increased the number of revertant colonies. In the nonactivation phase of the first trial, cytotoxicity to revertant colonies was observed at 187.5  $\mu\text{g}/\text{plate}$  for TA102 and TA100, and at 750  $\mu\text{g}/\text{plate}$  for WP2uvrA. Cytotoxicity to background lawn was observed at 375  $\mu\text{g}/\text{plate}$  for TA 1535 TA 100 and TA 98, 187.5  $\mu\text{g}/\text{plate}$  for TA 102 and 1500  $\mu\text{g}/\text{plate}$  for WP2uvrA. Microcolonies were noted at 750  $\mu\text{g}/\text{plate}$  for TA 1535 and TA98, 375  $\mu\text{g}/\text{plate}$  for TA100 and at 1500  $\mu\text{g}/\text{plate}$  for WP2uvrA. In the activation phase, cytotoxicity to revertant colonies was observed at 187.5  $\mu\text{g}/\text{plate}$  for TA102, and at 750  $\mu\text{g}/\text{plate}$  and above for TA1535 and WP2uvrA. Cytotoxicity to background lawn was observed at 1500  $\mu\text{g}/\text{plate}$  for TA1535, and 750  $\mu\text{g}/\text{plate}$  for TA98. Marked cytotoxicity to background lawn and microcolonies were noted at 500  $\mu\text{g}/\text{plate}$  for TA 100 and 102, and at 1500  $\mu\text{g}/\text{plate}$  for TA 1535. In the second trial, cytotoxicity to revertant colonies was observed at 93.8  $\mu\text{g}/\text{plate}$  for TA97a, 187.5  $\mu\text{g}/\text{plate}$  for TA102, 375  $\mu\text{g}/\text{plate}$  for TA100 and TA1535 and at 1500  $\mu\text{g}/\text{plate}$  for WP2uvrA. Cytotoxicity to background lawn was observed at 187.5  $\mu\text{g}/\text{plate}$  for TA102, 375  $\mu\text{g}/\text{plate}$  for TA100, 375  $\mu\text{g}/\text{plate}$  for TA97a and TA1535, 750  $\mu\text{g}/\text{plate}$  for TA98 and at 1500  $\mu\text{g}/\text{plate}$  for WP2uvrA. In the activation phase, cytotoxicity to revertant colonies was observed at 187.5  $\mu\text{g}/\text{plate}$  for TA102 and TA97a, 375  $\mu\text{g}/\text{plate}$  for TA98 and TA1535 and at 750  $\mu\text{g}/\text{plate}$  for TA100 and WP2uvrA. Cytotoxicity to background lawn was observed at 750  $\mu\text{g}/\text{plate}$  for TA97a, TA98, and TA100, and 1500  $\mu\text{g}/\text{plate}$  for TA1535 and WP2uvrA. In the third trial, concentrations of 93.8 and 187.5  $\mu\text{g}/\text{plate}$  were cytotoxic to revertant colonies of TA97a in the nonactivation and activation phases, respectively, while no toxicity to the background lawn was observed. A concentration of 750  $\mu\text{g}/\text{plate}$  was cytotoxic to both the revertant colonies and background lawn in strain TA100 in the activation phase.

Thus, SCH 34117 with added impurities and degradants was negative in the bacterial mutation test (Ames assay) using plate incorporation under the conditions tested, in concurrence with the sponsor's conclusion. The level of impurities, \_\_\_\_\_ exceed those proposed by the sponsor in the drug substance \_\_\_\_\_ respectively).

**Chromosome Aberration Study in Human Peripheral Lymphocytes***Schering Study No.:* 99241 ~~Study No.:~~ *Volume:* 10.8

*Study endpoint:* Clastogenicity  
*Study Dates:* Starting date November 8, 1999; report issued April 14, 2000  
*Testing Lab:* ~~\_\_\_\_\_~~  
*Test Article:* SCH 34117 (Batch 99-34117-X-202) diluted in 50% ethanol  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Methods:** A series of chromosome aberration assays were performed  $\pm$  metabolic activation (S9 fraction from Aroclor 1254-treated rats) using whole blood from a healthy female donor. Duplicate cultures were exposed to either negative controls, solvent control, doses of SCH 34117 (polymorph ratio: Form I (13%) and Form II (87%) adjusted in duplicate assays for toxicity) or doses of positive control. This study was performed as part of the sponsor's qualification for proposed specifications for synthesis impurities ~~\_\_\_\_\_~~ and degradants ~~\_\_\_\_\_~~ which were added to the administered drug. The test drug was dissolved in 50% ethanol, while the positive controls, mitomycin C (1-2  $\mu\text{g/ml}$ ; for the nonactivation assays) and cyclophosphamide (25-50  $\mu\text{g/ml}$ ; for the activation assays) were dissolved in sterile deionized water. Two assays were performed  $\pm$  metabolic activation:  $\sim$  4 hour treatment without metabolic activation followed by  $\sim$  22 hour harvest;  $\sim$  19 hour treatment without metabolic activation followed by  $\sim$  22 hour harvest; two independent assays with 4 hour treatment with metabolic activation followed by  $\sim$  22 hour harvest. The doses of SCH 34117 with impurities and degradants used for the initial assay were 0.037-600  $\mu\text{g/ml}$  and 0.313-50  $\mu\text{g/ml}$  in the confirmatory trial.

The mitotic index was assessed by analyzing the number of mitotic cells in 1000 cells/ culture. Cultures with a mitotic index  $<$  40% of the solvent control were not scored for chromosome aberrations. One hundred cells, if possible, were analyzed from each duplicate culture for chromosome aberrations at four dose levels of SCH 34117, the negative control, solvent control and at one dose level of the positive control. At least 25 cells were analyzed from those cultures with greater than 25% of cells with one or more aberrations. In addition, cells with polyploidy and endoreduplication from at least one hundred cells from each duplicate culture were analyzed. The assay was considered to be valid if negative and vehicle controls contain less than 5% cells with aberrations, the positive control result is significantly greater than vehicle control, the highest dose was selected based upon dose limits, solubility or cytotoxicity (50%) and the assay has three analyzable doses. A response was considered positive if the test article induced statistically significant increases in the number of cells with aberrations over those of the solvent controls at one or more concentrations in two donors and the increases showed a positive dose-response, or if the test article induced statistically significant increases in the number of cells with chromosome aberrations in at least two consecutive concentrations in two donors.

**Results:** Osmolality of the test sample was comparable to that of the solvent control. The pH of the test sample was 8.5 versus 8.0 for the solvent control. Under the conditions tested, SCH



**REPRODUCTIVE TOXICOLOGY:**

The sponsor submitted dose-ranging reproductive toxicology studies to IND 55,364. The definitive studies were submitted to this NDA and are reviewed below.

**Oral (gavage) fertility study of SCH 34117 in rats**

*Report No.:* P-6891      *Study No.:* 97112      *Volume:* 1.28

*Study Dates:* Starting date 10/28/1997; report issued 5/8/1999  
*Testing Lab:* Safety Evaluation Center; Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 34117 (Batch# 97-34117-X-02RA; purity = 99%) in 0.4% aqueous methylcellulose  
*Concentration:* 1.2-4.8 mg SCH 34117/ml  
*Dose Volume:* 5 ml/kg/day  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

The protocol for this study was not reviewed by the Division.

**Methods:** CrL:CD(SD)Br VAF/Plus rats (males: 10 weeks old; 315-399 g; females: 12 weeks old; 203-291 g) were assigned to the following treatment groups:

| Dose (mg/kg/day)      | 0  | 6  | 12 | 24 |
|-----------------------|----|----|----|----|
| No. of rats/sex/group | 25 | 25 | 25 | 25 |

Male rats were orally administered vehicle or SCH 34117 for 4 weeks prior to mating and at least until the end of the mating period (43-49 days). Doses were selected based upon a pilot study (P-6821, oral doses of 6, 24 and 48 mg/kg; see Original IND 55,364 review) and the lack of drug-related histopathologic effects on male reproductive organs in toxicity studies (1 month at up to 120 mg/kg/day). Female rats were dosed for 14 days prior to mating and throughout the mating period until day 7 of gestation. The following observations were made:

Clinical observation . . . 1 time daily  
 Body weight . . . . . Males: twice/week. Females: 2x/week through pre-mating and cohabitation and on days 0, 6, 10 and 14 of gestation.  
 Food consumption . . . . Once/week in males; once/week from first day of dosing through start of mating and days 0 to 6, 6 to 10, and 10 to 14 of gestation in females.  
 Estrus cycle . . . . . Vaginal cytology checked daily through confirmation of copulation.  
 Necropsy . . . . . gross external and visceral examination; males: paired testes and epididymal weights recorded;  
 Histopathology . . . . . males: testis from all males and epididymis from control and high dose animals as well as two mid-dose males with gross necropsy findings; females: uteri and ovaries exposed to collect reproduction data