

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-363**

**Pharmacology Review(s)**

**PHARMACOLOGY/TOXICOLOGY COVER SHEET**

Rec.  
2/15/02  
9:29AM

NDA number: 21-363

Review number: 1

Sequence number/date/type of submission: 000/April 10, 2001/Original NDA  
000/January 16, 2002/Labeling

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: January 29, 2002

**Drug:**

Trade Name: CLARINEX (Desloratadine) 5 mg Tablets

Generic: Descarboethoxyloratadine (DCL, SCH 34117)

Code Name: SCH 34117

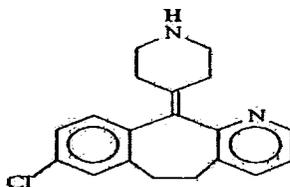
Chemical name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)

CAS registry number: NA

Mole file number: NA

Molecular formula/molecular weight: C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>/310.8

Structure:



Relevant INDs/NDAs/DMFs:

IND: /

IND: /

NDA 21-165 Clarinex (Seasonal allergic rhinitis)

NDA 21-297 Clarinex (chronic idiopathic urticaria)

NDA: /

NDA: /

NDA: /

Drug class: Anti-histamine

Indication: Allergic rhinitis

**Clinical formulation:**

<b>Ingredient: DCL layer</b>	<b>mg/tablet</b>
DCL micronized	5
Corn starch NF	
Dibasic calcium phosphate dihydrate USP	
Microcrystalline cellulose NF	
Talc USP	
Carnauba wax NF	
White wax NF	
Dye FD&C blue No. 2 aluminum lake	
<b>Nominal Tablet weight</b>	<b>106.61</b>

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

**Proposed use: Adults and 12 years of age and over: The recommended dose of Clarinex tablets is 5 mg once daily. In patients with liver failure or renal insufficiency, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data.**

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

**Studies reviewed within this submission: None.**

**Studies not reviewed within this submission: None**

**APPEARS THIS WAY  
ON ORIGINAL**

## *Executive Summary*

### I. Recommendations

#### A. Recommendation on Approvability

NDA 21-363 is approvable from a preclinical perspective.

#### B. Recommendation for Nonclinical Studies

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. This recommendation was communicated to the sponsor in the Approval letter for NDA 21-165.

#### C. Recommendations on Labeling

The sponsor's proposed labeling conforms to that for the recently approved Clarinex tablet (NDA 21-165) in terms of preclinical information and is acceptable.

### 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.

#### 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  
None at this time.

III. Administrative

A. Reviewer signature:

  
\_\_\_\_\_  
Timothy J. McGovern, Ph.D.

B. Supervisor signature:      Concurrence -

  
\_\_\_\_\_  
C. Joseph Sun, Ph.D.

C. cc: list:

A. Zeccola  
C.J. Sun  
T.J. McGovern

**TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW**

**I. PHARMACOLOGY: ..... 6**

**II. SAFETY PHARMACOLOGY: ..... 6**

**III. PHARMACOKINETICS/TOXICOKINETICS: ..... 8**

**IV. GENERAL TOXICOLOGY:..... 10**

**V. GENETIC TOXICOLOGY: ..... 11**

**VI. CARCINOGENICITY: ..... 12**

**VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: ..... 13**

**VIII. SPECIAL TOXICOLOGY STUDIES: ..... 14**

**IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:..... 14**

**X. APPENDIX/ATTACHMENTS:..... 16**

**APPEARS THIS WAY  
ON ORIGINAL**

## PHARMACOLOGY/TOXICOLOGY REVIEW

### I. PHARMACOLOGY:

All pharmacology studies were reviewed under IND  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  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 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-

<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.

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 ( $i_{Kr}$ ) 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 ( $i_{K1}$ ) 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.

APPEARS THIS WAY  
ON ORIGINAL

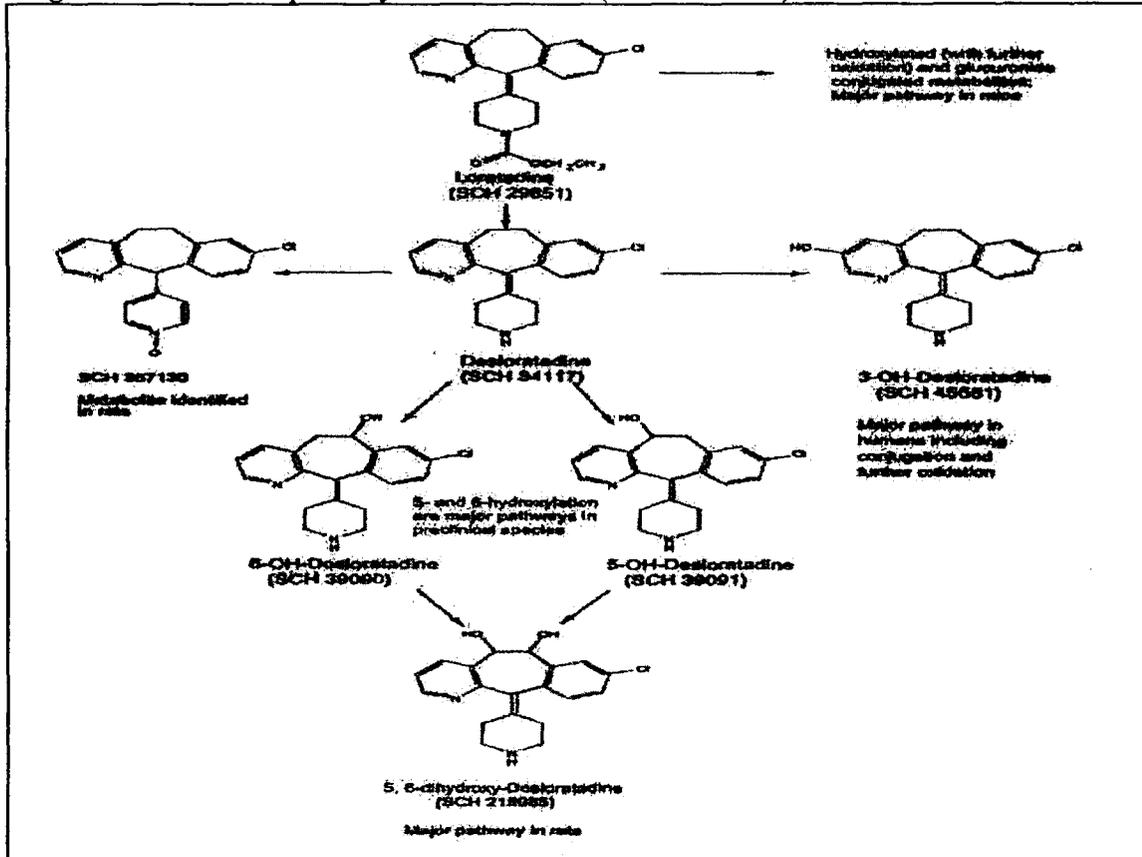
### III. PHARMACOKINETICS/TOXICOKINETICS:

All pharmacokinetic/toxicokinetic studies were reviewed under IND — and NDA 21-165. 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. 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.

APPEARS THIS WAY  
ON ORIGINAL

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



BEST POSSIBLE COPY

**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.

APPEARS THIS WAY  
ON ORIGINAL

#### IV. GENERAL TOXICOLOGY:

All toxicology studies were reviewed under IND — and NDA 21-165. See the attached reviews for the detailed study evaluations of the studies.

##### **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 —. Maximum non-lethal 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 non-lethal 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 finding 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.

*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.

**Toxicology conclusions:** The nonclinical safety of SCH 34117 has been adequately tested with the primary finding related to phospholipidosis.

**V. GENETIC TOXICOLOGY:**

All genetic toxicology studies were reviewed under IND [redacted] and NDA 21-165. See the attached reviews for the detailed study evaluations.

**Genetic toxicology summary:** Genetic toxicology studies assessing SCH 34117 were submitted to IND [redacted] 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.

**Labeling recommendations:** The label should state that SCH 34117 tested negatively in the assays performed for the standard battery.

APPEARS THIS WAY  
ON ORIGINAL

## 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 ~~\_\_\_\_\_~~ 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 \_\_\_\_\_ 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:** All nonclinical studies were submitted and reviewed in IND \_\_\_\_\_ 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. Therefore, chronic studies with SCH 34117 were not required. SCH 34117 tested negatively in the standard battery of genetic toxicology assays. 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.

**General Toxicology Issues:** The sponsor agreed to perform a 2-year mouse carcinogenicity assay as a Phase 4 commitment.

**Recommendations:**

1. The NDA for Clarinex 5 mg Tablets for the treatment of allergic rhinitis is approvable from a preclinical perspective.
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 proposed labeling is acceptable as it conforms to the approved labeling for NDA 21-165.

APPEARS THIS WAY  
ON ORIGINAL

**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

**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.**

**APPEARS THIS WAY  
ON ORIGINAL**

**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

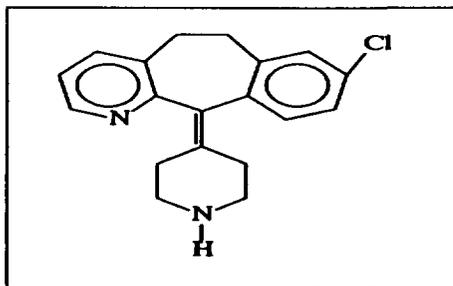
**Information to be Conveyed to Sponsor:** Yes (✓), No ( )

**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	
Blue	
Clear	
Carnauba wax NF	
White wax NF	
<b>Total tablet weight</b>	<b>106.61</b>

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

**Related INDs/NDAs:**

- IND |
- 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
- 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 #/ Reference #	Vol.
<b><i>New Pharmacology – Schering Study Reports:</i></b>		
Inhibition of <sup>3</sup> H-pyridylamine binding to the histamine H <sub>1</sub> -receptor by loratadine	SN 30372	1.7
Inhibition of <sup>3</sup> H-pyridylamine 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 α 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 C4 from human blood eosinophils.	SN 30854	1.8
Antissussive 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 FcεRI+ 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	SN 30063	1.8
Effects of loratadine metabolites on cardiovascular function in rats	P-5429	1.8
Electrocardiographic effects of intravenous SCH 34117 in the guinea pig	D-28578	1.8
The comparative effects of quinidine and non-sedating antihistamines on HERG (I Kr) channels expressed in <i>Xenopus</i> oocytes.	D-28717	1.8
One-week oral (gavage) cardiovascular study of SCH 34117 in cynomolgus monkeys	SN 98558	1.10
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	8	1.8
Effects of Sch 34117 on respiratory function in conscious rats.	SN 30650	1.8
<b><i>New Pharmacokinetic (ADME) Studies:</i></b>		

Study	Res. Report #/ Reference #	Vol.
SCH 34117: Pharmacokinetics, metabolism and excretion of <sup>14</sup> C-SCH 34117 following a 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/ 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/ 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	SN 99287	10.8
Chromosome aberration study of SCH 34117 with impurities and degradants in human peripheral blood lymphocytes	SN 99241	10.8
<b><i>New Reproductive Toxicology:</i></b>		
Oral (gavage) fertility study of SCH 34117 in rats	P-6891	1.28
Fertility study of SCH 34117 administered by oral gavage in male rats	SN 98552	1.29
Oral (gavage) embryo-fetal developmental toxicity and toxicokinetic study in rats	P-6922	1.31
Oral perinatal and postnatal development study of SCH 34117 in rats	SN 97117	1.33
Oral embryo-fetal development study of SCH 34117 in rabbits	P-6802	1.32

**Previously Reviewed Preclinical Studies in IND ' 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. Ducic, 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	P-6771	1.9	5/22/1998
Single-dose intraperitoneal administration, mice	P-6772	1.9	5/22/1998
Single-dose oral administration, rats	P-6769	1.9	5/22/1998
Single-dose intraperitoneal administration, rats	P-6770	1.9	5/22/1998
Oral (gavage) rising-dose tolerance study of SCH 34117 in cynomolgus monkeys	P-6808	1.9	5/22/1998
<b>Multiple Dose Toxicology:</b>			
Two-week oral safety profile study of SCH 34117 in rats.	D-18289	1.10	5/22/1998
Two-week oral (gavage) range-finding toxicity and toxicokinetic study of	P-6526	1.11	5/22/1998

Study	Res. Report #	Vol.	Date of Review
SCH 34117 and SCH 29851 in rats.			
Two-week oral (gavage) range-finding toxicity study of SCH 34117 and SCH 29851 with toxicokinetics in cynomolgus monkeys.	P-6527	1.14	5/22/1998
Four-week oral (gavage) toxicity study of SCH 34117 in rats.	P-6965	1.17	10/27/1998
Four-week oral (gavage) toxicity study of SCH 34117 in cynomolgus monkeys.	P-6974	1.19	10/27/1998
Three-month oral (gavage) toxicity study of SCH 34117 in rats.	P-6973	1.23	1/31/2000
Three-month oral (gavage) toxicity study of SCH 34117 in cynomolgus monkeys.	P-6976	1.26	1/31/2000
<b>Genetic Toxicology Studies:</b>			
Bacterial mutagenicity study of SCH 34117.	P-6609	1.34	5/22/1998
Chromosome aberration study of SCH 34117 in human peripheral blood lymphocytes.	P-6692	1.35	5/22/1998
Mouse bone marrow erythrocyte micronucleus study of SCH 34117.	P-6912	1.35	1/31/2000
<b>Reproductive Toxicology:</b>			
Pilot oral (gavage) fertility study of SCH 34117 in rats.	P-6821	1.28	5/22/1998
Pilot oral embryo-fetal development study of SCH 34117 in rats.	P-6718	1.31	5/22/1998
Dose-range finding study of SCH 34117 in female rabbits.	P-6719	1.32	5/22/1998
Pilot (oral) perinatal and postnatal development study of SCH 34117 in rats	P-6817	1.33	12/15/1998

**Studies Submitted but Not Reviewed in this NDA Submission:**

Study	Res. Report #	Vol.	Reference #
1			

7

*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            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.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 1. Receptor binding assays:**

Cell/Model type	Report #/ 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. 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.  <table border="1"> <thead> <tr> <th>Compound</th> <th></th> <th>Ki (nM)</th> </tr> </thead> <tbody> <tr> <td>SCH 34117</td> <td>DCL</td> <td>7.0</td> </tr> <tr> <td>SCH 39090</td> <td>6-OH DCL</td> <td>4.5</td> </tr> <tr> <td>SCH 39091</td> <td>5-OH DCL</td> <td>9.5</td> </tr> <tr> <td>SCH 45581</td> <td>3-OH DCL</td> <td>13</td> </tr> <tr> <td>SCH 354202</td> <td>3-OH DCL gluc</td> <td>19% at 2 μM</td> </tr> </tbody> </table>	Compound		Ki (nM)	SCH 34117	DCL	7.0	SCH 39090	6-OH DCL	4.5	SCH 39091	5-OH DCL	9.5	SCH 45581	3-OH DCL	13	SCH 354202	3-OH DCL gluc	19% at 2 μM									
Compound		Ki (nM)																											
SCH 34117	DCL	7.0																											
SCH 39090	6-OH DCL	4.5																											
SCH 39091	5-OH DCL	9.5																											
SCH 45581	3-OH DCL	13																											
SCH 354202	3-OH DCL gluc	19% at 2 μM																											
Various species target receptors	D-28718	<table border="1"> <thead> <tr> <th>Receptor type</th> <th>IC50 (nM)</th> <th>Ki (nM)</th> </tr> </thead> <tbody> <tr> <td>Histamine H1, central</td> <td>17</td> <td>5.7</td> </tr> <tr> <td>Histamine H1, peripheral</td> <td>168</td> <td>13</td> </tr> <tr> <td>Histamine, H2</td> <td>360</td> <td>353</td> </tr> <tr> <td>Muscarinic M1</td> <td>208</td> <td>50</td> </tr> <tr> <td>Muscarinic M2</td> <td>131</td> <td>47</td> </tr> <tr> <td>Muscarinic M4</td> <td>493</td> <td>104</td> </tr> <tr> <td>Muscarinic M5</td> <td>445</td> <td>320</td> </tr> <tr> <td>Serotonin 5-HT7</td> <td>369</td> <td>204</td> </tr> </tbody> </table>	Receptor type	IC50 (nM)	Ki (nM)	Histamine H1, central	17	5.7	Histamine H1, peripheral	168	13	Histamine, H2	360	353	Muscarinic M1	208	50	Muscarinic M2	131	47	Muscarinic M4	493	104	Muscarinic M5	445	320	Serotonin 5-HT7	369	204
Receptor type	IC50 (nM)	Ki (nM)																											
Histamine H1, central	17	5.7																											
Histamine H1, peripheral	168	13																											
Histamine, H2	360	353																											
Muscarinic M1	208	50																											
Muscarinic M2	131	47																											
Muscarinic M4	493	104																											
Muscarinic M5	445	320																											
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.

APPEARS THIS WAY  
ON ORIGINAL

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

Cell/Model type	Report #/ 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. Both drugs inhibited superoxide anion production by monocytes induced by PMA or zymosan at > 0.1 and 1 $\mu$ M, respectively. 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: Similar inhibition of P-selectin expression ( $IC_{50}$ = $13 \times 10^{-9}$ M and $23 \times 10^{-9}$ M, respectively). IL-6 and IL-8 inhibition: SCH 34117 displayed greater potency ( $IC_{50}$ = $2.6 \times 10^{-12}$ M and $10^{-9}$ M, respectively) than loratadine ( $IC_{50}$ = $0.3 \times 10^{-6}$ 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 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 ( $IC_{30}$ = 6-11 $\mu$ mol/L). Higher SCH 34117 concentrations induced mediator release. 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. Inhibition by loratadine increased when extracellular $Ca^{2+}$ reduced from 1.8 to 0.45 $\mu$ M. Both drugs (2.5-25 $\mu$ M) inhibited the cytosolic $Ca^{2+}$ 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. 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. 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. 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 ( $IC_{50}$ = 0.035-0.12 $\mu$ M).
Inhibition of RANTES release in nasal polyp epithelial cell line	5	SCH 34117 and loratadine (10 $\mu$ M, added 15 minutes prior to activation) significantly reduced RANTES release (~ 70% and 40%, respectively) 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. <u>Compound</u> <u>ED50 (µg)</u> <u>Max. efficacy/concentration</u> Levocabastine    0.025              85%/1 µg SCH 34117        0.9                  69%/3 µg Loratadine        8.7                  49%/10 µg
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 µM) failed to significantly alter HERG currents. 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). 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
<b>Cardiovascular effects</b>		
Conscious, 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.
	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.
Cynomolgus monkeys	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 <u>Plasma levels:</u> Males Day 0: 50.3 ng/ml at 4 mg/kg; 456 ng/ml at 12 mg/kg; Day 6: 84.1 ng/ml at 4 mg/kg; 1041 ng/ml at 12 mg/kg; Females Day 0: 153 ng/ml at 4 mg/kg, 199 ng/ml at 12 mg/kg. 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 Ltk- cell lines transfected with human	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

cardiac Kv1.5K+ channel complementary DNA, HERG cardiac K+ channels from <i>X. laevis</i> oocyte		was enhanced at membrane potentials near threshold relative to higher potentials but did not alter the kinetics of Kv1.5 current activation or deactivation. Mouse Ltk-: Loratadine (3 $\mu$ M) reduced the mean probability of Kv1.5 channel opening by reducing the number of openings in bursts and burst duration. HERG K+: Loratadine (10 $\mu$ M) 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 $\mu$ M) 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). Relative potency at 1 $\mu$ M: terfenadine>quinidine>ebastine>loratadine = SCH 34117
CNS: 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.
Gastrointestinal: 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.
Renal: Rat	SN 30063	Renal: SCH 34117 (4 or 12 mg/kg, po): No effect on urinary excretion of Na+ or K+ 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.

APPEARS THIS WAY  
ON ORIGINAL

**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	
C <sub>max</sub> (ng equiv/ml)	807	504	132	291	
T <sub>max</sub> (hr)	6	8	3	8	
AUC (tf) (ng equiv.hr/ml)	11919	8492	1047	3500	
T <sub>1/2</sub> (hr)	NA	NA	2.05	2.83	
F (%)	NA	NA	45	94	
F <sub>a</sub> (%)	74	82	NA	NA	
CL/F (L/hr.kg)	NA	NA	6.63	1.99	
Parameters	IV administration				
	C <sub>max</sub> (ng equiv/ml)	1027	889	569	583
	T <sub>max</sub> (hr)	3	0.25	0.25	0.25
	AUC (tf) (ng equiv.hr/ml)	15890	10046	2300	3637
	T <sub>1/2</sub> (hr)	NA	NA	2.26	2.53
	V <sub>area</sub> (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
C <sub>max</sub> (ng equiv/ml)	1030	775	73.1	42.1	141	261
T <sub>max</sub> (hr)	2	82	1	0.5	2	3
AUC (tf) (ng equiv.hr/ml)	18863	13028	200	136	1523	2661
T <sub>1/2</sub> (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			
Cmax (ng equiv/ml)	519	542	505
Tmax (hr)	4	1	1
AUC (tf) (ng equiv.hr/ml)	7290	6941	7115
SCH 34117 in plasma			
Cmax (ng/ml)	319	310	278
Tmax (hr)	1	2	1
AUC(tf) (ng.hr/ml)	2502	2412	2449
T1/2 (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			
Cmax (ng equiv/ml)	2134	1879	1817
Tmax (hr)	0.5	1	0.5
AUC (tf) (ng equiv.hr/ml)	15120	19910	17560
SCH 29851 in plasma			
Cmax (ng/ml)	67	53.1	52.8
Tmax (hr)	0.5	0.25	0.25
AUC(tf) (ng.hr/ml)	87.6	70.1	78.1
T1/2 (hr)	1.37	1.04	1.18
Cl/F (L/hr.kg)	97	121	109
SCH 34117 in plasma			
Cmax (ng/ml)	117	65.8	89.3
Tmax (hr)	3	1	3
AUC(tf) (ng.hr/ml)	805	584	705
T1/2 (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 Cmax 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 Cmax. 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												
C <sub>max</sub> (ng/ml)	864	830	969	1443	928	1362	2060	2238	1378	1512	7815	6356
T <sub>max</sub> (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												
C <sub>max</sub> (ng/ml)	629	1061	275	579	963	1350	407	653	1129	1614	383	994
T <sub>max</sub> (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												
C <sub>max</sub> (ng/ml)	733	1008	765	986	832	1130	1112	1482	946	1190	1679	1928
T <sub>max</sub> (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: 30 mg/kg SCH 34117			Administered: 72 mg/kg SCH 29851			Administered: 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> (ng/ml)	953	1680	1270	293	399	284	1790	2250	1890
AUC (0-24) (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.**

Analyte	C <sub>max</sub> (ng/ml)			AUC(0-24) (ng.hr/ml)		
	Males	Females	Combined	Males	Females	Combined
	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: 30 mg/kg SCH 34117		Administered: 48 mg/kg SCH 29851		
	Analyte: SCH 34117	Analyte: 3-OH-SCH 34117	Analyte: SCH 29851	Analyte: SCH 34117	Analyte: 3-OH-SCH 34117
C <sub>max</sub> (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) (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	% 14C-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 [redacted] 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 (0-48 hr)		Urine (0-48 hr)		Feces (0-96 hr)	
Major metabolites	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>
Monooxy-SCH 34117-Glu	2	4	30	20	7	15	<1	<1	-- <sup>b</sup>	-- <sup>b</sup>
OH-SCH 34117-Glu	4	5	<1	5	<1	2	2	2	-- <sup>b</sup>	-- <sup>b</sup>
di-OH-SCH 34117-Glu	3	5	1	3	1	1	<1	<1	-- <sup>b</sup>	-- <sup>b</sup>
3-OH-SCH 29851-Glu	13	17	2	8	3	<1	<1	<1	-- <sup>b</sup>	-- <sup>b</sup>
OH-SCH 29851-Glu	12	25	10	25	16	1	1	<1	-- <sup>b</sup>	-- <sup>b</sup>
di-OH-SCH 29851-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).

APPEARS THIS WAY  
ON ORIGINAL

**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%) SCH 39090 (7%) SCH 39091 (8%) OH-SCH 34117-glucuronide (7%) SCH 218985 (66%)	SCH 29851 (5%) SCH 34117 (2%) SCH 39090 (5%) SCH 39091 (8%) OH-SCH 34117-glucuronide (12%) SCH 218985 (52%)	SCH 34117 (2%) SCH 39090 (22%) SCH 39091 (19%) SCH 357130 (10%) SCH 218985 (25%)	SCH 29851 (4%) SCH 34117 (7%) SCH 39090 (19%) SCH 39091 (20%) SCH 357130 (6%) SCH 218985 (19%) Unknowns (19%)
Mouse	SCH 34117 (32%) SCH 39090 (11%) SCH 39091 (38%)	SCH 29851 (7%) SCH 34117 (2%) SCH 39090 (13%) SCH 39091 (44%) OH-SCH 29851-glucuronide (14%)	SCH 34117 (79%) SCH 39090 (4%) SCH 39091 (11%) Unknown D (4%)	SCH 29851 (15%) SCH 34117 (12%) SCH 39090 (9%) SCH 39091 (11%)  3-OH-SCH 29851 (<1%) 5-OH-SCH 29851 (<5%) 6-OH-SCH 29851 (<8%) dihydroxy-SCH 29851 (16%) Unknowns (18%)
Rabbit	SCH 34117 (2%) SCH 39090 (18%) SCH 39091 (58%)	SCH 29851 (10%) SCH 34117 (<1%) SCH 39090 (11%) SCH 39091 (53%) 3-OH-SCH 34117-glucuronide (8%)	SCH 34117 (<1%) SCH 39090 (44%) SCH 39091 (44%) SCH 45581 (<1%)	SCH 34117 (<1%) SCH 39090 (35%) SCH 39091 (58%) SCH 45581 (<1%)
Monkey	SCH 34117 (8%) SCH 39090 (37%) SCH 39091 (16%) OH-SCH 34117-glucuronide (21%) Monooxy-SCH 34117-glucuronide (11%)	SCH 29851 (5%) SCH 34117 (3%) SCH 39090 (17%) SCH 39091 (13%) OH-SCH 34117-glucuronide (39%) Monooxy-SCH 34117-glucuronide (6%)	SCH 34117 (51%) SCH 39090 (25%) SCH 39091 (23%)	SCH 29851 (<1%) SCH 34117 (38%) SCH 39090 (19%) SCH 39091 (43%)
Human	SCH 34117 (97%) SCH 39090 (<1%) SCH 39091 (<1%) SCH 45581 (3%)	SCH 29851 (7%) SCH 34117 (75%) SCH 39090 (5%) SCH 39091 (9%) SCH 45581 (3%)	SCH 34117 (96%) Unknown D (4%)	SCH 29851 (19%) 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  $\mu$ M) in rat and mouse liver microsomes and S9 fractions from normal and arochlor-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  $\mu$ 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 [REDACTED]. 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 [REDACTED] 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 \_\_\_\_\_ 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