CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-312

PHARMACOLOGY REVIEW(S)

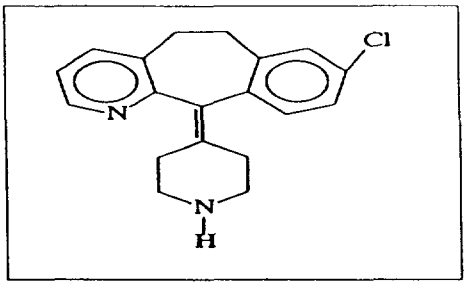
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-312
Review number: 1
Serial number/date/type of submission: NA/December 21, 2000/Original NDA
Information to be Conveyed 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 Completed: October 15, 2001

Drug:

Trade Name: CLARINEX RediTabs
Generic: Descarboethoxyloratadine (DCL)
Code Name: SCH 34117
Chemical name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinyllidene)
CAS registry number: NA
Mole file number: NA
Molecular formula/molecular weight: $C_{19}H_{19}ClN_2$/310.8
Structure:



Relevant INDs/NDAs/DMFs:

IND [ ] Descarboethoxyloratadine tablets
IND [ ] Descarboethoxyloratadine RediTabs
NDA 21-165 Clarinex (Seasonal allergic rhinitis)
NDA 21-297 Clarinex (chronic idiopathic urticaria)
NDA [
NDA]
NDA 21-363 Clarinex (Allergic rhinitis)

Drug Class: Anti-histamine

Indication: Seasonal allergic rhinitis and treatment of chronic idiopathic urticaria

Clinical Formulation:

Ingredient	(mg/tablet)
Desloratadine (SCH 34117),	5
Gelatin type B NF	
Mannitol USP	
Aspartame NF	
Polacrilin potassium USP	
Dye red	
Flavor tutti-frutti	
Citric acid USP	

Route of Administration: Oral

Proposed use: Adults and 12 years of age and over: 5 mg once daily. In a 50 kg adult this is equivalent to 0.1 mg/kg or 3.7 mg/m^2

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

Studies submitted and reviewed in this submission:
Study "**SN 99290:** Mucous membrane irritation study of SCH 34117 (desloratadine) RediTab Tablets in the hamster cheek pouch" was submitted to IND and reviewed (see Review #2, attached).

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ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability
NDA 21-312 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.

C. Recommendations on Labeling
The sponsor will be requested to submit updated labeling to conform, where applicable, to the final labeling for NDA 21-165 with the addition of text relating to the indication of chronic idiopathic urticaria. Thus, a review of the product label will be performed at a later time.

II. Summary of Nonclinical Findings

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

B. Pharmacologic Activity
SCH 34117 demonstrated a high selectivity for H_1-receptors over H_2 or H_3-receptors. This finding was confirmed in isolated guinea pig lung tissue.

C. Nonclinical Safety Issues Relevant to Clinical Use
No nonclinical safety issues relevant to clinical use were identified.

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TABLE OF CONTENTS – PHARMACOLOGY/TOXICOLOGY REVIEW

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_1-receptors over H_2 or H_3-receptors and displayed a 14-fold greater affinity for the H_1-receptor than loratadine in cloned H_1 human receptor subtypes (IC_{50} = 51 and 721 nM, respectively). This finding was confirmed in isolated guinea pig lung tissue (IC_{50} = 840 and 3030 nM for SCH 34117 and loratadine, respectively). SCH 34117 was also ~ 18-fold more potent than loratadine in rat brain H_1-receptor activity (SCH 34117 K_i = 4.8-7 nM) and was comparable in potency to its primary unconjugated metabolites. In an *in vitro* assessment of antihistaminic activity using guinea pig isolated ileum, SCH 34117 was up to 20-fold more potent than loratadine and was 4 to 8.5-fold more potent in inhibiting histamine-induced bronchospasm *in vivo* (SCH 34117 ED_{50} = 0.11-0.27 mg/kg, IV). *In vivo* studies performed for the loratadine program demonstrated that SCH 34117 was 2.5-4 times more potent than loratadine following oral administration in mice and guinea pigs. SCH 34117 also expressed a high affinity for cloned human M_1 and M_3 receptor subtypes (IC_{50} = 48 and 125 nM). In a separate study, SCH 34117 showed greatest activity at central H_1 receptors (IC_{50} = 17 nM) while activity at peripheral H_1 receptors was similar to that at M_2 muscarinic receptors (IC_{50} = 131-168 nM). Other receptor sites tested showed significantly reduced activity. Thus, the results in the Clinical Pharmacology of the labeling submitted by the sponsor 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[1], loratadine (30 and 100 mg/kg, IV) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 µg/ml), in contrast to terfenadine, quinidine and diphenhydramine which induced significant cardiovascular and ECG effects. Resulting SCH 34117 concentrations (1.46 µg/ml) were 370-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

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

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

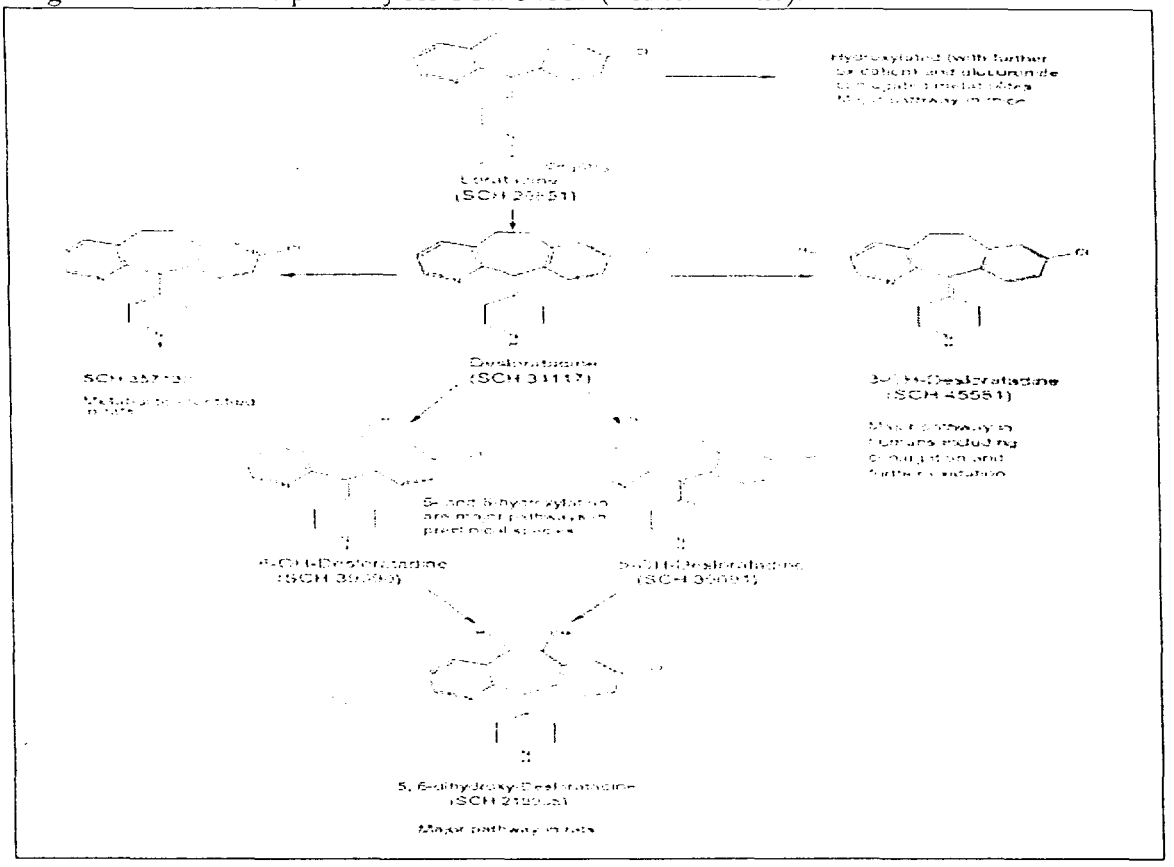
III. PHARMACOKINETICS/TOXICOKINETICS:

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-portionally. Following loratadine administration, systemic exposure to SCH 34117 was greater in all species tested except for rabbits. Tmax was achieved within 4 hours in rabbits, mice and monkeys and 1.5-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. Drug accumulation was evident and no gender differences were observed. In rats, SCH 34117 was widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. 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.

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



IV. GENERAL TOXICOLOGY:

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

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 nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS and respiratory system in rats and mice and the gastrointestinal system in monkeys.

Subchronic Toxicity: Studies were conducted in rats and monkeys for up to 3 months duration with both SCH 34117 and loratadine in order to support a bridging strategy to the loratadine chronic toxicology program. The primary toxicity findings in both species,

similar to loratadine, was systemic phospholipidosis in organ systems throughout the body. The kidney and epididymides were target organs in rats.

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

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

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.

Safety evaluation of exicpients: A number of excipients are included in the formulation for Clarinex RediTabs that were not included in the Claritin RediTab formulation. These include aspartame, polacrilin potassium, Dye — red —— and Flavor tutti-frutti ——— The former two ingredients are acceptable, as they have been used in approved products indicated for similar treatment duration and indication severity at higher levels than those currently proposed. The ———— for the latter two ingredients were considered found to be adequate for support of the current application. The ingredients gelatin, mannitol and citric acid are found at ———— in the current formulation than in the formulation for Claritin RediTabs. However, the proposed levels are acceptable as they are below previously approved levels in products indicated for similar treatment duration and indication severity.

V. GENETIC TOXICOLOGY:

All genetic toxicology studies were reviewed under IND —— 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 —— 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 [redacted] These studies also produced negative results.

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 listed above.

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 DEVLOPMENTAL TOXICOLOGY:

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

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

An oral peri- and post-natal study was performed in rats. A dose of 3 mg/kg SCH 34117 (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients

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

Reproductive and developmental toxicology conclusions: SCH 34117 induced a male-specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes at an oral dose of 12 mg/kg. An increase in pre-implantion 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.

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

VIII. SPECIAL TOXICOLOGY STUDIES:

One mucosal irritation assay was submitted to NDA 21-312. This study was reviewed under IND ——— (see attached review #2). Drug-related observations included very slight to slight redness in all female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab from the first day of dosing onward. Severity did not increase with dosing duration. One drug-treated animal died and the death was attributed to a possible toxic effect of the drug with the isoflurane anesthesia. No drug-related gross or microscopic findings were noted. The findings of this study indicate that the proposed SCH 34117 RediTab formulation does not pose a significant irritancy risk in the intended population.

Conclusions: The findings of the mucosal irritation study indicate that the proposed SCH 34117 RediTab formulation does not pose a significant irritancy risk in the intended population.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: With the exception of a mucosal irritation study using the proposed RediTab formulation, 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-implantion 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. This comment was communicated to the sponsor in the approvable letter for NDA 21-165 and should be communicated again at this time.

Recommendations:

1. The NDA for Clarinex RediTabs for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria is approvable from a preclinical perspective pending acceptable updates to the proposed product label.

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

Labeling with basis for findings: The review team decided to postpone review of the product label pending submission of updated label by the sponsor. Wording in the label concerning the indication of chronic idiopathic urticaria is based upon clinical data and is, thus, not subject to review from a preclinical perspective.

Reviewer signature: _____

Supervisor signature: _____

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X. APPENDIX/ATTACHMENTS:

Addendum to review:
NDA 21-165 Original Review
NDA 21-165 Label Review #1
Addendum to NDA 21-165 Label Review #1
IND ——— Review #2

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

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

KEY WORDS: Anti-histamine

NDA No. 21-165

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

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

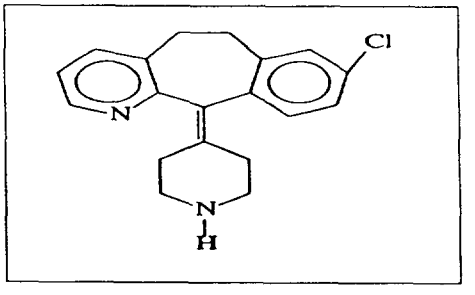
Information to be Conveyed to Sponsor: Yes (✔), No ( )

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

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

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

Structure:



Empirical Formula: $C_{19}H_{19}ClN_2$

Molecular Weight: 310.82

Drug Class: Anti-histamine

Indication: Seasonal allergic rhinitis

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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^2.

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	
Total tablet weight	**106.61**

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)

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Preclinical Studies Submitted and Reviewed in this NDA:

Study	Res. Report # Reference #	Vol.
New Pharmacology – Schering Study Reports:		
Inhibition of ^{3}H-pyrilamine binding to the histamine H_1-receptor by loratadine	SN 30372	1.7
Inhibition of ^{3}H-pyrilamine binding to the histamine H_1-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 Ascaris challenge in allergic cynomolgus monkeys.	D-28686	1.8
New Pharmacology – Publications and References:		
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 H1-antagonist, desethoxycarbonyl-loratadine. J Allergy Clin Immunol. 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. Biochem Pharmacol. 1994; 47: 789-794.	2	1.7
Genovese A, Patella V et al. Loratadine and desethonycarbonylloratadine inhibit the immunological release of mediators from human FcεRI+ cells. Clin Exp Allergy. 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 H1-antagonist decarboethoxyloratadine and dexamethasone by human mast and basophil cell lines. Exp Dermatol. 1995; 4: 272-276	4	1.7
Lebel B, Bousquet J et al. Loratadine reduces RANTES release by an epithelial cell line. J Allergy Clin Immunol. 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. J Allergy Clin Immunol. 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. Clin Exp Allergy. 1997; 27: 1167-1174.	7	1.7
New Safety Pharmacology Studies and Publications:		
Ancillary pharmacology of SCH 34117		
Effects of loratadine metabolites on cardiovascular function in rats	SN 30063	1.8
Electrocardiographic effects of intravenous SCH 34117 in the guinea pig	P-5429	1.8
The comparative effects of quinidine and non-sedating antihistamines on HERG (I Kr) channels expressed in Xenopus oocytes.	D-28578 D-28717	1.8 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. Mol. Pharmacol. 52, 314-322, 1997	8	1.8
Effects of Sch 34117 on respiratory function in conscious rats.		

Study	Res. Report #/ Reference #	Vol.
New Pharmacokinetic (ADME) Studies:	SN 30650	1.8
SCH 34117: Pharmacokinetics, metabolism and excretion of ^{14}C-SCH 34117 following a single oral dose to male and female mice.	SN 97308	1.36
SCH 29851: Pharmacokinetics, metabolism and excretion of ^{14}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 ^{14}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 ^{14}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 ^{14}C-SCH 34117 following a single oral or intravenous dose to the male and female cynomolgus monkeys.	SN 97309/	1.51
SCH 29851: Pharmacokinetics, metabolism and excretion of ^{14}C-SCH 29851 following a single oral dose to the male and female cynomolgus monkeys.	SN98452 SN 97312/	1.53
SCH 34117: Toxicokinetic study of single oral (gavage) dose of SCH 34117 or SCH 29851 in cynomolgus monkeys.	SN 98452 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
New Genetic Toxicology Studies:		
Bacterial mutagenicity study of SCH 34117 with impurities and degradants		
Chromosome aberration study of SCH 34117 with impurities and degradants in human peripheral blood lymphocytes	SN 99287 SN 99241	10.8 10.8
New Reproductive Toxicology:		
Oral (gavage) fertility study of SCH 34117 in rats		
Fertility study of SCH 34117 administered by oral gavage in male rats	P-6891	1.28
Oral (gavage) embryo-fetal developmental toxicity and toxicokinetic study in rats	SN 98552	1.29
Oral perinatal and postnatal development study of SCH 34117 in rats	P-6922	1.31
Oral embryo-fetal development study of SCH 34117 in rabbits	SN 97117 P-6802	1.33 1.32

Previously Reviewed Preclinical Studies in IND ——— and Submitted in this NDA:

Study	Res. Report #	Vol.	Date of Review
Pharmacology – Schering Study Reports:			
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
Pharmacology – Publications and References:			
Handley DA, McCullough JR, Fang Y et al. Descarboethoxyloratadine, a metabolite of loratadine, is a superior antihistamine. Ann. Allergy Asthma and Immunol. 1997; 78: 143.		1.7	5/22/1998
Cardelus, Puig J, Bou J et al. Xerostomia and mydriasis; two possible muscarainic peripheral side effects associated with descarboethoxyloratadine, the main metabolite of loratadine. Proc Br Pharmacol Soc. 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. Clin Exp Allergy. 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 + channels. J. Cardiovasc. Pharmacol 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. Br. J. Pharmacol.122 796-798, 1997			
Safety Pharmacology:	30523	1.8	6/7/2000
Effect of loratadine and its metabolite, descarboethoxyloratadine, on the QT interval in the isolated perfused rabbitheart model (Langendorff)	SN 30416	1.8	6/7/2000
Effect of desloratadine (SCH 34117) on electrophysiological properties of guinea pig ventricular muscle.	SN 30417	1.8	6/7/2000
Effect of loratadine (SCH 29851) and desloratadine (SCH 34117) on Na+ current in rabbit ventricular myocytes.	SN 30418	1.8	6/7/2000
Effect of loratadine (SCH 29851) and desloratadine (SCH 34117) on Ikr and IK1.			
Pharmacokinetics:	D-28407	1.36	5/22/1998
Summary of metabolic profiling (SCH 34117 and SCH 29851) data from SPRI pilot studies in rat, mouse and monkey.	P-6527	1.55	12/15/1998
SCH 34117: Toxicokinetic study of single oral (gavage) dose of SCH 34117 or SCH 29851 in cynomolgus monkeys.	P-6741		6/7/2000
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 ^{14}C-SCH 34117			
Acute Toxicology:	P-6771	1.9	5/22/1998
Single-dose oral administration, mice	P-6772	1.9	5/22/1998
Single-dose intraperitoneal administration, mice	P-6769	1.9	5/22/1998
Single-dose oral administration, rats	P-6770	1.9	5/22/1998
Single-dose intraperitoneal administration, rats	P-6808	1.9	5/22/1998
Oral (gavage) rising-dose tolerance study of SCH 34117 in cynomolgus monkeys			
Multiple Dose Toxicology:	D-18289	1.10	5/22/1998
Two-week oral safety profile study of SCH 34117 in rats.	P-6526	1.11	5/22/1998

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

Studies Submitted but Not Reviewed in this NDA Submission:

Study	Res. Report # Reference #	Vol.
[redacted]		

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

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

PHARMACOLOGY:

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

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

Table 1. Receptor binding assays:

Cell/Model type	Report #/ Reference	Activity
Rat brain membrane	SN 30372	SCH 34117 was ~ 20-fold more potent than loratadine, but comparable to chlorpheniramine, in inhibiting binding of [^{3}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 [^{3}H]pyrilamine to rat brain H1 receptor while the conjugated glucuronide of the 3-OH-DCL metabolite displayed reduced potency by over 100-fold. 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	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.

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 μM with almost complete inhibition at 50 μM. Both drugs inhibited superoxide anion production by monocytes induced by PMA or zymosan at > 0.1 and 1 μM, 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 (IC50= $13x10^{-9}$ M and $23x10^{-9}$ M, respectively). IL-6 and IL-8 inhibition: SCH 34117 displayed greater potency (IC50 = $2.6x10^{-12}$ M and 10^{-9} M, respectively) than loratadine (IC50 = $0.3x10^{-6}$ M and $0.2x10^{-6}$ M, respectively)
Inhibition of chemotaxis, and leukotriene and superoxide production in human eosinophils and secretion of interleukins and TNF-α by monocytes	SN 30854	Eosinophils: Attenuated chemotaxis in response to PAF with maximum attenuation of 36% at 10 μM and adhesion (25% at 10 μM). No effect noted on leukotriene production at a concentration of 10 μM. 10 μM inhibited PMA-stimulated and spontaneous superoxide generation Monocytes: SCH 34117 (100 nM to 10 μM) did not inhibit secretion of IL-4, -5, -13, -10, -1B, -16 and TNF-α 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 (IC30 = 6-11 μmol/L). Higher SCH 34117 concentrations induced mediator release. Rapid onset of inhibition at 10 μmol/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 μM SCH 34117 and 7 μM loratadine in anti-IgE triggered human basophils and DNP-triggered rat basophilic leukemia cells. Inhibition by loratadine increased when extracellular Ca2+ reduced from 1.8 to 0.45 μM. Both drugs (2.5-25 μM) inhibited the cytosolic Ca2+ rise induced by DNP-BSA challenge in rat cells which may inhibit mediator release.
Inhibition of histamine, LTC4, PGD2 and tryptase release in human FcεRI+ cells from peripheral blood, skin or lung tissue	3	SCH 34117 and loratadine (3x10-6 to 10-4 M) inhibited release of histamine and LTC4 (5-40%) following pre-incubation before Der p 1 antigen or anti-FcεRI challenge. 10-40% inhibition of histamine and LTC4 and PGD2 release from lung tissue cells activated by anti-FcεRI. 10-40% inhibition of histamine, tryptase, LTC4 and PGD2 release from skin cells challenged with anti-FcεRI.
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-α production in human peripheral blood cells	D-28727	Weak inhibitory activity against TNF-α production (7-24% at 0.1 to 10 μM) following LPS-stimulation. Rolipram significantly more potent (IC50 = 0.035-0.12 μM).
Inhibition of RANTES release in nasal polyp epithelial cell line	5	SCH 34117 and loratadine (10 μm, added 15 minutes prior to activation) significantly reduced RANTES release (~ 70% and 40%, respectively) induced by TNF-α. Spontaneous RANTES release was not significantly

		affected.
Inhibition of IL-4 and IL-13 secretion in human basophils	D-30853	SCH 34117 (10-7 to 10-5 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 LTC4 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. Compound / ED50 (µg) / Max. efficacy/concentration 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_{HERG} current (15-20%) compared to terfenadine and quinidine (IC50 = 82 and 168 nM, respectively). SCH 34117 had no effect on the gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg in rats.

Table 4. Summary of safety pharmacology studies.

Model	Study # / Reference #	Results
Cardiovascular effects		
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 Plasma levels: 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 (IC50 = 5.6x10-6 M vs 8.08x10-7 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 *X. laevis* 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 μM) reduced the mean probability of Kv1.5 channel opening by reducing the number of openings in bursts and burst duration. HERG K+: Loratadine (10 μM) failed to significantly alter HERG currents over wide range of test potentials.
Human HERG (Ikr) channels expressed in Xenopus oocytes	D-28717	Loratadine and SCH 34117 (up to 10 μM) had minimal effects on I_{HERG} current (15-20%) compared to terfenadine and quinidine (IC50 = 82 and 168 nM, respectively). Relative potency at 1 μM: 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 ht post-dosing.
Renal: Rat	SN 30063	Renal: SCH 34117 (4 or 12 mg/kg, po): No effect on urinary excretion o 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 ^{14}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.

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

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

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

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

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

In the cynomolgus monkey, a similar dose of ^{14}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
	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 ^{14}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 ^{14}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 ^{14}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												
Cmax (ng /ml)	864	830	969	1443	928	1362	2060	2238	1378	1512	7815	6356
Tmax (hr)	12	6	12	2	6	12	6	8	8	12	1.5	8
AUC (0-24) (ng.hr ml)	14592	16970	17275	27393	18982	24907	44060	44969	25676	29206	114828	119641
R	NA	NA	1.18	1.61	NA	NA	2.32	1.81	NA	NA	4.47	4.1
Administered drug: SCH 29851; Analyte: SCH 29851												
Cmax (ng /ml)	629	1061	275	579	963	1350	407	653	1129	1614	383	994
Tmax (hr)	1.5	0.5	1	1	2	0.5	1	1	4	1	1.5	1.5
AUC (0-24) (ng.hr ml)	3042	3051	1365	2171	6372	10089	2206	6139	12728	21994	3985	11309
R	NA	NA	0.45	0.71	NA	NA	0.35	0.61	NA	NA	0.31	0.51
Administered drug: SCH 29851; Analyte: SCH 34117												
Cmax (ng /ml)	733	1008	765	986	832	1130	1112	1482	946	1190	1679	1928
Tmax (hr)	4	6	4	8	8	6	2	4	8	6	8	1
AUC (0-24) (ng.hr ml)	10826	14644	11740	18655	14565	20401	20340	31510	19602	24670	36700	37268
R	NA	NA	1.08	1.27	NA	NA	1.4	1.54	NA	NA	1.87	1.51

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

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

Parameters	Administered: 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
Cmax (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.

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

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

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

Parameters	Administered: 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
Cmax (ng/ml)	459	1.43	855	169	0.605
Tmax (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	Cmax (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[a]	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[c]	9	6	1	8	11	9	12	37	8	12	12	21
SCH 39091[d]	5	5	2	5	7	9	12	25	5	8	12	16
SCH 218985[e]	<1	6	3	<1	<1	<1	27	15	7	4	7	5
SCH 357130[f]	38	49	62	3	5	8	<1	<1	<1	<1	--[b]	--[b]
SCH 356467[g]	4	3	4	2	<1	5	<1	<1	<1	<1	2	<1
Unknown C1-C6	5	10	13	<1	--[b]	--[b]	<1	--[b]	5	<1	--[b]	--[b]

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[a]	6	12	1	6	12	M	F	M	F	M	F
SCH 29851	17	6	<1	16	3	3	<1	<1	--[b]	--[b]	2	2
SCH 34117	13	16	9	33	37	31	4	2	1	2	8	10
SCH 39090[c]	8	10	11	5	10	14	6	21	7	10	14	18
SCH 39091[d]	5	9	8	3	10	4	8	23	8	8	17	23
SCH 218985[e]	4	7	14	<1	<1	<1	18	19	7	4	7	5
SCH 357130[f]	21	29	48	4	14	17	<1	<1	<1	<1	--[b]	--[b]
SCH 356467[g]	2	5	5	2	2	9	<1	<1	--[b]	--[b]	2	<1
Unknown C1-C6	4	6	1	2	3	7	--[b]	--[b]	<1	<1	--[b]	<1
Metabolite H	--[b]	--[b]	--[b]	--[b]	--[b]	--[b]	3	3	--[b]	--[b]	2	3
Unknowns 11-12	--[b]	--[b]	--[b]	--[b]	--[b]	--[b]	16	16	--[b]	--[b]	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[a]	12	4	12	M	F	M	F	M	F
SCH 34117	25	22	23	9	7	6	<1	<1	2	5
SCH 39090[c]	7	8	10	5	9	13	4	3	10	19
SCH 39091[d]	4	3	4	5	14	23	2	2	12	19
SCH 39090-Glu	8	7	10	4	4	<1	3	4	--[b]	--[b]
SCH 39091-Glu	17	19	28	13	7	4	6	6	--[b]	--[b]
Monooxy-SCH 34117-Glu	3	2	9	36	29	38	1	<1	--[b]	--[b]
OH-SCH 34117-Glu	21	20	3	<1	11	2	2	3	--[b]	--[b]
di-OH-SCH 34117-Glu	3	3	<1	7	7	7	<1	<1	--[b]	--[b]

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[a]	12	4	12	M	F	M	F	M	F
SCH 29851	2	<1	4	<1	<1	<1	--[b]	--[b]	11	1
SCH 34117	2	3	8	3	2	3	<1	<1	2	2
SCH 39090[c]	1	3	3	<1	12	13	3	4	12	14
SCH 39091[d]	4	2	12	<1	32	53	3	3	20	28
SCH 39090-Glu	7	4	6	4	3	<1	3	5	--[b]	--[b]
SCH 39091-Glu	17	13	<1	12	2	3	12	13	--[b]	--[b]
Monooxy-SCH 34117-Glu	2	4	30	20	7	15	<1	<1	--[b]	--[b]
OH-SCH 34117-Glu	4	5	<1	5	<1	2	2	2	--[b]	--[b]
di-OH-SCH 34117-Glu	3	5	1	3	1	1	<1	<1	--[b]	--[b]
3-OH-SCH 29851-Glu	13	17	2	8	3	<1	<1	<1	--[b]	--[b]
OH-SCH 29851-Glu	12	25	10	25	16	1	1	<1	--[b]	--[b]
di-OH-SCH 29851-Glu	3	<1	3	5	3	<1	<1	<1	--[b]	--[b]
Unknowns K1-K3	6	<1	10	<1	<1	<1	<1	<1	4	8
Unknown-K-Glu	2	2	3	1	9	6	2	2	--[b]	--[b]

a: blood collection time b: not detected
c: 6-OH-SCH 34117 d: 5- OH-SCH 34117

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

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

	Radioactivity											
	% of chromatogram								% of dose			
	Male plasma			Female plasma			Bile (4 hr)		Urine (0-48 hr)		Feces (0-48 hr)	
Major metabolites	1[a]	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[c]	3	4	<1	2	5	<1	2	10	7	7	9	8
SCH 39091[d]	5	13	14	7	8	<1	19	40	24	22	17	19
Unknown D[e]	15	13	7	20	14	<1	--[b]	--[b]	--[b]	--[b]	--[b]	--[b]

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, descarboethoxylation and glucoronidation (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[a]	4	12	1	4	12	M	F	M	F	M	F
SCH 29851	4	2	--[b]	6	1	--[b]	--[b]	--[b]	--[b]	--[b]	3	3
SCH 34117	15	13	6	9	7	7	3	3	2	<1	5	3
SCH 39090[c]	6	2	--[b]	<1	<1	--[b]	1	2	4	7	8	9
SCH 39091[d]	17	10	--[b]	1	2	--[b]	3	8	11	14	16	15
5- or 6-OH-SCH 29851	16	9	8	22	7	<1	--[b]	--[b]	--[b]	--[b]	5	2
5- or 6-OH-SCH 29851-Glu	--[b]	--[b]	--[b]	--[b]	--[b]	--[b]	9	10	--[b]	--[b]	--[b]	--[b]
3-OH-SCH 29851	<1	<1	--[b]	2	3	--[b]	2	3	--[b]	--[b]	7	17
3-OH-SCH 29851-Glu	23	35	75	30	46	93	22	22	--[b]	--[b]	--[b]	--[b]
di-OH-SCH 29851-Glu	1	--[b]	--[b]	3	--[b]	--[b]	42	36	--[b]	--[b]	--[b]	--[b]

a: blood collection time b: not detected
c: 6-OH-SCH 34117 d: 5- OH-SCH 34117

In vitro studies: In vitro metabolism of ^{14}C-SCH 29851 (0.26 μM) and ^{14}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 µM) in rat and mouse liver microsomes and S9 fractions from normal and aroclor-treated animals. SCH 29851 was converted to SCH 34117 in both species and both drugs yielded SCH 39090 and 39091. At a low substrate concentration (0.3 µM), 3-hydroxy SCH 34117 (SCH

45581) was not detected in any preparation. However, at 35 µM 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 µM 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 ———. 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 ——— 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-Nitroflourene	(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 x 10^8 cells/ml for bacterial strains and ~ 15 x 10^8 cells/ml for *E. coli*, the mean number of revertant colonies/plate in the solvent control was within the range of the historical solvent control values of the same strain and the mean number of induced revertants/plate in the positive controls was at least three-fold greater than the mean of its concurrent solvent control for TA 1535, and at least two-fold greater than the mean of their respective concurrent controls for *E. coli* and other *Salmonella* strains. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in at least one of the six tester strains, the magnitude of increase was at least two-fold above the solvent control for strains TA 97A, TA

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

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

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

APPEARS THIS WAY
ON ORIGINAL

Chromosome Aberration Study in Human Peripheral Lymphocytes

Schering Study No.: 99241 *Study No.:* [redacted] *Volume:* 10.8

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

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

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

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

34117 did not induce chromosomal aberrations, polyploidy or endoreduplication in cell cultures with or without metabolic activation at doses up to 37.5 µg/ml (4 hour treatment/22 hour harvest without metabolic activation), 25 µg/ml (19 hour treatment/22 hour harvest without metabolic activation), and 60-70 µg/ml (3 hour treatment/22 hour harvest with metabolic activation). Doses above those cited induced cytotoxicity which lead to mitotic indices < 40% or reduced cell count (sparse numbers of attached cells) and these cultures were not assessed for chromosomal aberrations. Increased incidences of chromosome aberrations were observed in cultures dosed with the positive control agents, cyclophosphamide and mitomycin C. Negative and solvent controls were within historical ranges.

SCH 34117 with added impurities and degradants was negative for inducing chromosome aberrations in cultured whole blood human lymphocytes under the conditions tested with or without exogenous metabolic activation system at doses up to 70 µg/ml SCH 34117. The level of impurities. [redacted] exceed those proposed by the sponsor in the drug substance [redacted] respectively).

CARCINOGENICITY:

Carcinogenicity studies have not been performed with SCH 34117. The sponsor requested a waiver from performing carcinogenicity studies with SCH 34117 based upon SCH 34117 exposure ratios achieved during carcinogenicity studies performed with loratadine. CDER's Pharmacology/Toxicology Senior Policy Team concluded that the rat carcinogenicity study performed with loratadine sufficiently assessed the carcinogenic liability of SCH 34117 but the sponsor would be required to perform a two-year mouse carcinogenicity study as a Phase 4 commitment. This issue is discussed in greater detail in the Overall Summary and Evaluation.

REPRODUCTIVE TOXICOLOGY:

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

Oral (gavage) fertility study of SCH 34117 in rats
Report No.: P-6891 *Study No.*: 97112 *Volume*: 1.28

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

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

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

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

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

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

Reproduction parameters . . . . . Copulated females sacrificed on day 14 of gestation; assessment for number of corpora lutea, implantation sites, live/dead fetuses, and resorptions, distribution of fetuses in the uterus, fertility indices, precoital interval, male and female mating index, dead embryos, sex of fetus, weight of fetus/placenta

Statistics . . . . . Deemed unnecessary.

Results:

Mortality: No deaths were reported.

Clinical Observations: Fecal changes were observed at all dose levels and included enlarged fecal pellets and reduced number of fecal pellets. Observations increased with increasing dose. Small sized stool was noted at the mid- and high-doses and no stool observed at the high-dose. Soft stool was also noted in 1-2 animals/sex at each dose level.

Body Weight: Mean body weights in females were reduced compared to dosing day 1 in all groups after 3 days dosing (Day 17) with mid- and high-dose groups demonstrating greater losses (7 and 11.5 g, respectively) than control animals (Table 25). By the seventh day of dosing (Day 21), all groups had recovered except for high dose animals (reduced by 0.8 g). By dosing day 14 (Day 28), all groups were comparable. Body weight gain from day 0-6 of gestation was reduced by 28% and 40% in mid- and high-dose dams, respectively. Over the entire dosing period, body weight gain was reduced by 35% in high-dose dams. Absolute body weight was reduced by 8% over the same time period. Body weight gain in males was not affected throughout the study.

Table 25: Summary of effects on body weight in females.

Dose (mg/kg)	0	6	12	24
Premating BW gain (g)				
Day 17	-3.7	-2.2	-7	-11.5
Day 21	no change	2.6	0.6	-0.8
Day 28	9.5	7.6	10.2	8.3
Gestation BW gain				
Day 0-6 - % Δ from control		-6	-28	-40
Day 0-14 - % Δ from control		-6	-13	-22
BW gain over entire dosing period: (Day 14 Premating – Day 6 Gestation) % Δ from control		-19	-14	-35

Food Intake: Food consumption was reduced by 19% in high-dose dams after the first week of dosing but recovered in the second week. Mean food consumption was again reduced by 17% after gestation day 7 but recovered thereafter. No significant findings were noted in males.

Estrus cycle: No drug-related effects were observed.

Necropsy: No drug-related effects on organ weights (testis or epididymis) or macroscopic findings were noted. However, histologic examination of the reproductive organs revealed an

increased incidence of mild spermatic cellular debris at the high dose (10 of 25 males vs 5 of 25 control animals).

Reproductive parameters: Fertility indices were not affected. However, pre-implantation loss was increased in a dose-dependent manner compared to control animals and the number of implantation sites and fetuses were reduced at the high dose (Table 26). The increased pre-implantation loss at the mid-dose was within historical control values. These findings indicate an embryocidal effect of SCH 34117.

Table 26: Summary of effects on reproductive parameters.

Dose (mg/kg)	0	6	12	24
Pre-implantation loss %/animal	1.3	2.2	9.6	17.2
Implantation sites #/animal	15.1	13.9	13.9	11.2
Fetuses #/animal	14.1	13	12.9	10.5

Key study observations: The NOAEL for fertility effects was > 24 mg/kg; a NOAEL of 12 mg/kg in females and males was identified for "general toxicity findings". Effects at the high dose included increased pre-implantation loss, decreased numbers of implantation sites and fetuses, and an increased incidence of mild spermatic cellular debris.

Oral (gavage) fertility study of SCH 34117 in male rats
Study No.: ——— *Volume*: 1.29

Study Dates: Starting date 12/16/1998; report issued 8/4/1999
Testing Lab: ———
Test Article: SCH 34117 (Batch# 97-34117-X-03-RA; purity = 100%) in 0.4% aqueous methylcellulose
Concentration: 0.6-8 mg SCH 34117/ml
Dose Volume: 5 ml/kg/day
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

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

Methods: CrL:CD(SD) Br rats (males: 11 weeks old; 301-412 g; females: 12 weeks old; 202-348g) were assigned to the following treatment groups:

Dose (mg/kg/day)	0	3	12	40
No. of male rats/group – main	25	25	25	25
No. of male rats/group – 18 week recovery	15	0	0	15

Male rats were orally administered vehicle or SCH 34117 for 70 days prior to mating and throughout the mating period until euthanasia (total dosing period 106-108 days). Doses were selected based upon results of a pilot study (P-6821, see Original IND ——, review) and the fertility study reviewed above. Female rats (25/dose group) were not dosed during this study. The report stated that recovery data would be submitted as an addendum to final report. This data was submitted to IND —— Serial # 159 (dated June 23, 2000) and is reviewed currently. During the mating period, each female was placed in cohabitation with a male for a maximum of 14 days. The following observations were made:

Clinical observation	Males: at least 1 time daily. Females: once weekly.
Body weight	Males: twice/week. Females: weekly until confirmed mating, then on days 0, 7, and 14 of gestation.
Food consumption	twice/week in males; not measured in females.
Necropsy	Males euthanized ~ 25 days after confirmed mating, females euthanized on day 14 of gestation. Gross external and visceral examination; males: brain, pituitary gland, prostate gland, testes and epididymal weights recorded. Females: uteri and ovaries exposed to collect reproduction data
Histopathology	males: coagulating gland, prostate gland, seminal vesicles, testis and epididymis from all males
Reproduction parameters	Copulated females sacrificed on day 14 of gestation; assessment for number of corpora lutea, implantation sites, live/dead embryos, and resorptions (early/late), distribution of implantation sites, resorptions, and embryos in the uterus. Male mating and fertility indices, and precoital interval were calculated.
Sperm analysis	sperm collected from all rats to assess motility. Left testis used to determine spermatid count and sperm count determined from left epididymis.
Statistics	Two-tailed tests with analysis of variance, Dunnett's test, Kruskall-Wallis test and Mann-Whitney U-test.

Results:

Mortality: No drug related effects were noted in males. One low-dose male was euthanized in extremis on study day 65 due to malaligned upper incisors and 36% body weight loss. One non-mated female each from the mid-dose and high-dose groups were euthanized on days 93 and 14, respectively.

Clinical Observations: No drug-related effects were noted.

Body Weight: Body weight gain in high-dose males was reduced from study day 21 onward. Following the premating period, body weight gain was reduced by 29%; body weight gain was reduced by 35% following the last day of dosing (Table 27). At the end of the recovery period, no significant difference in body weight gain or absolute body weight was observed between the control and high-dose groups.

Table 27: Summary of effects on body weight gain.

Dose (mg/kg)	3	12	40
Body weight gain			
Premating period - %Δ from control	-3	-9	-29
End of dosing - %Δ from control	-8	-11	-35
End of recovery - %Δ from control			3

Food Intake: Food consumption was consistently reduced in high-dose males up to 19%. No differences between the control and high-dose groups were noted during the recovery period.

Necropsy: Reductions in absolute organ weights were noted in the prostate, testes, epididymis, and cauda epididymis, primarily at the high dose (Table 28). Similar findings were observed in relative organ to body weight in the prostate, and testes though not in the other organs listed. These findings were not recoverable. Gross examination revealed bilateral small and soft testes at the mid- and high-doses, and pale pituitary and small prostate at the high dose. Findings in the testes were not reversible. There was no histopathologic correlate for the prostatic findings.

Table 28: Summary of findings at necropsy in male rats.

	Dose (mg/kg)				
	0	3	12	40	40-Recov
)solute organ weight changes					
Prostate: % Δ from control		14	-13	-33	-17
Right testis: % Δ from control		-1	-11	-38	-36
Left testis: % Δ from control		-3	-15	-42	-45
Right epididymis: % Δ from control		-3	-10	-19	-24
Left epididymis: % Δ from control		-1	-14	-21	-29
Right cauda epididymis: % Δ from control		-2	-16	-23	-25
Left cauda epididymis: % Δ from control		1	-21	-27	-31
acroscopic observations					
N =	25	25	25	25	15
Right testis					
Small	0	0	4	14	8
Soft	0	0	5	14	7
Left testis					
Small	0	1	6	16	10
Soft	0	1	7	17	10
Left epididymis					
Enlarged	0	0	0	1	0
Pituitary					
Pale	0	0	0	1	0
Prostate					
Small	0	0	0	2	0
Urinary bladder					
Thickened	0	0	0	1	0
Adipose tissue					
Necrotic	0	0	0	1	0

Histopathology: Histologic examination of the reproductive organs revealed dose-related degeneration of the seminiferous tubules, spermatid giant cells, epithelial spematogenic droplets, spermatid retention and seminiferous tubule atrophy in the testes (Table 29). Additional findings in the epididymis included vacuolation, spermatic cellular debris, oligospermia and hyperplasia. With the exception of spermatic cellular debris, these findings were not observed in the previously reviewed fertility study at doses up to 24 mg/kg, possibly due to the shorter duration of dosing. Following the recover period, most findings were only minimally reversible.

Table 29: Summary of histopathologic findings in male rats.

Dose (mg/kg)	0	3	12	40	40-Recovery
croscopic observations					
N =	25	24	25	25	15
Right testis					
Degeneration, seminiferous tubules					
Minimal	0	1	8	2	1
Mild	0	1	1	3	1
Moderate	0	0	0	2	1
Severe	0	0	4	14	7
Spermatid giant cells					
Minimal	0	0	1	0	0
Mild	0	1	1	4	0
Moderate	0	0	0	1	0
Droplets, spermatogenic, epithelium					
Minimal	0	1	0	2	0
Mild	0	0	0	2	0
Retention, spermatid					
Minimal	0	2	9	4	1
Atrophy, seminiferous tubule, focal					
Minimal	0	0	1	0	1
Mild	0	1	1	4	1
Moderate	0	0	0	0	1
Atrophy, seminiferous tubule, diffuse					
Moderate	0	0	0	1	0
Severe	0	0	4	14	7
Alteration, spermatogenic epithelium					
Minimal	0	0	0	2	1
Mild	0	0	1	3	1
Moderate	0	0	0	2	0
Right Epididymis					
Vacuolation, cytoplasmic, epithelial					
Minimal	0	0	0	13	5
Mild	0	0	0	2	0
Moderate	0	0	0	1	0
Cellular debris, spermatic					
Minimal	0	1	7	0	2
Mild	0	1	1	1	2
Moderate	0	0	1	19	1
Severe	0	0	4	0	0
Oligospermia					
Mild	0	0	1	0	2
Moderate	0	0	0	4	1
Severe	0	0	4	15	6
Hyperplasia					
Minimal	0	0	0	7	3

Mild	0	0	0	0	4
Pituitary gland					
Vacuolation – cytoplasmic, Rathke's					
Pouch, macrophage					
Minimal	2			11	3

Sperm analysis: Mean sperm numbers in the testis and epididymis and mean sperm production in the testis were reduced at the mid- and high-doses while reductions were also observed in 2 animals of the low-dose group (Table 30). Likewise, the percentage of motile sperm was also dose-dependently reduced in SCH 34117-treated animals with mid- and high-dose groups showing a 25.5% and 58.6% reduction compared to control animals. Following the recovery period, sperm numbers remained reduced at a level comparable to those at the end of the main study period while sperm motility appeared to almost fully recover.

Table 30: Summary of spermatogenic endpoints.

Dose (mg/kg)		0	3	12	40	0-Rec	40-Rec
erm numbers (# of sperm in millions/gram of tissue)							
Left testis –	mean values	77.6	78.4	60.8	20.3	93	31.3
	% change from control		1	-22	-74		-74
Left epididymis -	mean values	446.3	462.4	271	134.7	354.5	155.4
	% change from control		4	-39	-70		-56
Sperm motility (%)							
Motile sperm		84	75.8	58.5	25.4	84.3	75.6

Reproductive parameters: Male mating indices were comparable among all treatment groups (96-100%; Table 31). However, male fertility indices were reduced at the mid and high doses (76 and 37.5%, respectively compared to 100% and 95.8% in control and low-dose animals) and were associated with reduced sperm numbers and motility at these doses. Fertility indices were unaffected in a previous study up to 24 mg/kg but with a shorter dosing duration. Mean pre-coital intervals were comparable between groups. Following the recovery period, mating index in treated males was reduced but was similar to the mean historical control value (89.3%). The fertility index was only minimally improved following the recovery period.

Table 31: Summary of effects on reproductive parameters in males.

	Dose (mg/kg)					
Parameter	0	3	12	40	0-Rec	40-Rec
Male mating index (%)	100	100	96	96	100	87-93
Male fertility index (%)	100	95.8	76	37.5	93-100	54-57

One female in the mid- and high-dose groups showed no evidence of mating. Mean numbers of implantation sites, and viable embryos were reduced at the mid- and high-doses compared to control values, and the incidence of pre-implantation loss was increased at the high dose (Table

32). The litter proportion of early resorptions at the high dose (27.9%) was increased relative to control (6.7%) but may be due to the low numbers of females showing implantations due to adverse effects on sperm in males. No significant differences were observed in reproductive parameters between the two recovery groups.

Table 32: Summary of effects on reproductive parameters in females.

	Dose (mg/kg)			
Parameter	0	3	12	40
Viable embryos	15.4	13.9	12.4	7.9
Implantation sites	16.2	14.4	13.4	9.1
Pre-implantation loss	1.8	3.9	3.7	7.2

Shaded area indicates statistically significant difference from control value.

Key study observations: The NOAEL for fertility effects was 3 mg/kg; a NOAEL was not identified in males for general toxicity findings due to histological findings at all doses tested in the reproductive organs. Most findings were not reversible following an 18 week recovery period.

Oral (gavage) embryo-fetal developmental toxicity and toxicokinetic study of SCH 34117 in rats

Report No.: P-6922 *Study No.*: 97114 *Volume*: 1.31

Study Dates:	Starting date 9/12/1997; report issued 5/9/1999
Testing Lab:	Safety Evaluation Center, Schering Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch# 97-34117-X-02RA; purity = 99%) in 0.4% aqueous methylcellulose
Concentration:	1.2-9.6 mg SCH 34117/ml
Dose Volume:	5 ml/kg/day
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

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

Methods: female rats (11 weeks old; 227-307 g) were assigned to the following treatment groups:

Dose (mg/kg/day)	0	6	24	48
No. of teratology females	25	25	25	25
No. of toxicokinetic females	0	9	9	9

Each female rat was cohabitated with a breeder male on a one-to-one basis until positive evidence of mating was observed. Female rats in which copulation was confirmed received a daily oral dose of vehicle or test drug once daily on days 6 through 15 of gestation in order to assess its effects on dams, fetuses and offspring. The following observations were made:

Dams:

Clinical observation . . . daily examination of mated females
Body weight . . . . . Days 0, 6, 9,12, 15, 18 and 21 of gestation
Food consumption . . . . Days 0 to 6, 6 to 10, 10 to 15 and 15 to 21 of gestation
Blood collection . . . . . bled at 4, 8, and 24 hours post dose on gestation day 15
Necropsy . . . . . mated females sacrificed on gestation day 21; uteri and contents removed and weighed, dams examined for external and visceral changes
Reproduction parameters . . . . . determination of number of implantation sites, corpora lutea, fetuses (live/dead), and resorptions, distribution of fetuses in the uterus.

Fetuses (F_1):

External exam . . . . . abnormal conditions, sexed, body weights
Skeletal/Soft tissue exam . . . . . 50% of fetuses from each litter fixed and examined for soft tissue defects, kidneys graded for hydronephrosis. Remaining fetuses examined for gross visceral changes and skeletal examination.
Dead fetuses and resorptions . . examined grossly for external defects and for visceral and skeletal defects.

Statistical analysis: Continuous data analyzed by ANOVA; categorical data analyzed Chi-square test

Results:

Dams:

Mortality: One mid-dose dam died due to a dosing accident.

Clinical Observations: Drug-related clinical observations included reduced numbers of fecal pellets, large fecal pellets or no stool in mid- and high-dose animals.

Body Weight: Maternal body weight gain was dose-dependently reduced compared to control animals during the dosing period by 12%, 56%, and 92% at the low, mid and high doses, respectively (significant at the mid and high doses).

Food Intake: Food consumption was reduced during gestation days 6 to 10 in mid- and high-dose dams by 33% and 53%, respectively, compared to control animals. The reduction was 14% and 27%, respectively, from days 10 to 15 and values were comparable to controls once dosing ended.

Necropsy: No drug-related effects were noted.

Reproduction Parameters: No drug-related effects on reproduction parameters were noted. However, fetal body weight was reduced at mid- and high-doses by 8% and 10%, respectively, and may be related to the observed maternal toxicity at these doses.

Toxicokinetics: Systemic exposure to SCH 34117 under the dosing conditions of this study are summarized in Table 33. Exposure increased sub-proportionally with increasing dose and Tmax

was achieved within 24 hours. Mean plasma concentrations at 24 hours were 28-69% of the respective Cmax values indicating slow elimination of SCH 34117.

Table 33: Systemic exposure to SCH 34117 following oral administration.

	Dose (mg/kg)		
Parameter	6	24	48
Cmax (ng/ml)	487	1569	2468
Tmax (hr)	8	4	8
AUC(0-24 hr) (ng.hr/ml)	7875	31606	49238

Fetuses (F1):

Skeletal and visceral examination: No drug-related findings were noted following examination for gross or skeletal malformations. Skeletal variations were observed at the mid- and high-doses and consisted of unossified/reduced bone ossification in cervical vertebral centra, sternebra, and proximal phalanges of the paws (Table 34) and may be related to the observed maternal toxicity and reduced fetal growth *in utero* as indicated by reduced fetal weight in these dose groups.

Table 34: Summary of effects on skeletal variations in fetuses: total (%)

	Dose (mg/kg)			
Observation	0	6	24	48
Cervical vertebral centra unossified				
-fetal incidence	39 (22.8)	41 (23)	56 (35.2)	80 (46)
-litter incidence	16 (66.7)	15 (62.5)	15 (68.2)	21 (84)
Sternebra unossified				
-fetal incidence	2 (1.2)	1 (0.6)	19 (11.9)	18 (10.3)
-litter incidence	2 (8.3)	1 (4.2)	8 (36.4)	10 (40)
Sternebra reduced ossification				
-fetal incidence	12 (7)	16 (9)	30 (18.9)	35 (20.1)
-litter incidence	7 (29.2)	10 (41.7)	16 (72.7)	18 (72)
Shortened ribs				
-fetal incidence	0	0	1 (0.6)	5 (2.9)
-litter incidence	0	0	1(4.5)	2 (8)
Unossified proximal phalanges, hind paws				
-fetal incidence	69 (40.4)	63 (35.4)	75 (47.2)	124 (71.3)
-litter incidence	18 (75)	19 (79.2)	18 (81.8)	24 (96)
Total skeletal				
-fetal incidence	108 (63.2)	102 (57.3)	117 (73.6)	147 (84.5)
-litter incidence	23 (95.8)	22 (91.7)	22 (100)	24 (96)

Shaded area indicates statistically significant difference from control value.

Key study observations: A NOAEL of 48 mg/kg was identified for teratologic effects while 6 mg/kg was identified for developmental toxicity based upon reduced fetal weights and skeletal variations at the mid and high doses. The NOAEL for maternal toxicity was 6 mg/kg and was based upon reduced body weight gain and food consumption at the two highest doses. The decreased fetal weight and delayed ossification may be secondary to the maternal toxicity.

Oral embryo-fetal development study of SCH 34117 in rabbits

Report No.: P-6802 *Study No.*: 97116 *Volume*: 1.32

Study Dates:	Starting date 9/29/1997; report issued 5/17/1998
Testing Lab:	Safety Evaluation Center, Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch# 97-34117-X-02RA; purity = 99%; Batch# 97-11001-139; purity = 100%) in 0.4% aqueous methylcellulose
Concentration:	7.5-30 mg SCH 34117/ml
Dose Volume:	2 ml/kg/day
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

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

Methods: New Zealand white rabbits (5-6 months old; 2.91 – 3.99 kg) were assigned to the following treatment groups:

Nominal Dose (mg/kg/day)	0	15	30	60
No. of copulated females – main study	20	20	20	20
No. of copulated females – plasma analysis	0	3	3	3

Females were mated with males with day of mating designated as Day 0 of pregnancy. Females in which copulation was confirmed received a daily dose of vehicle or test drug by gastric intubation (gavage) once daily on days 7 through 19 of gestation. The following observations were made:

Dams:

Clinical observation . . . daily
Body weight . . . . . Days 0, 7, 10, 13, 16, 19, 22, 25, 28, and 30 after mating.
Food consumption . . visual estimate recorded daily gestation days 0-30
Blood collection . . . . . bled at 1, 3, 12 and 24 hours post dose on gestation day 19
Necropsy . . . . . mated females sacrificed on gestation day 30; uteri and contents removed, dams examined for external and visceral changes
Reproduction parameters . . . . . determination of number of implantation sites, corpora lutea, fetuses (live/dead), and resorptions, distribution of fetuses in the uterus.

Fetuses (F_1):

External exam . . . . . abnormal conditions, body weights assessed at necropsy
Morphologic exam . . . fetuses internally sexed, assessed for gross visceral changes, and skeletal examinations.
Dead fetuses and resorptions . . examined grossly for external defects and for visceral and skeletal defects.

Statistical analysis . . . . Continuous data analyzed by ANOVA; categorical data analyzed Chi-square test