Summary of Reproductive Toxicology Studies: Oral fertility studies with SCH 34117 in rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a peri- and post-natal development study in rats were submitted to this NDA by the sponsor. Doses were selected based upon pilot studies which were submitted to the IND. In the initial fertility study (6, 12, and 24 mg/kg), treatment-related effects were noted and included clinical signs at all doses (enlarged and reduced numbers of fecal pellets, small, soft or no stool), reduced body weight gain at the mid and high doses (14-35%), reduced food consumption in high-dose dams (17-19%) and microscopic observations in high-dose males (mild spermatic cellular debris). No effects on fertility were observed although preimplantation loss was increased and numbers of implantation sites and fetuses were decreased at the high dose. The NOAEL for fertility effects was > 24 mg/kg; a NOAEL of 12 mg/kg was identified for general toxicity findings. A second fertility study was performed in which males only were dosed (3, 12 and 40 mg/kg) for 106-108 days. General findings included reduced body weight gain and food consumption at the high-dose (35% and 19%, respectively), reduced organ weights at the high-dose (prostate, testis, epididymis; 19-42%), small and soft testes at all doses, microscopic findings at all doses including atrophy and degeneration of the seminiferous tubules, spermatid giant cells, spermatic cellular debris and oligospermia, and reduced sperm numbers (22-74%), production and motility (25-59%) at the mid- and high-doses. While mating indices were comparable at all doses, fertility indices were reduced at the mid- and high-doses by 24 and 63.5%, respectively. The number of implantation sites and viable embryos were also reduced in females mated with mid- and high-dose males and the incidence of preimplantation loss was increased. The NOAEL for fertility effects in males in this study was 3 mg/kg while a NOAEL of < 3 mg/kg was identified for general toxicity findings.

An embryo-fetal development study in rats (6, 24 and 48 mg/kg) produced similar clinical signs in dams as in the fertility study as well as reduced body weight gain (56-92%) and food intake (up to 53%) at the mid- and high-doses. No drug-related effects were observed on reproduction parameters although fetal body weight was reduced 8-10% at the mid- and high-doses. There were no skeletal or visceral malformations although skeletal variations were observed at the mid- and high-doses (unossified/reduced ossification of vetebra, sternebra and proximal phalanges). These effects, however, could be due to the observed maternal toxicity. Thus, a NOAEL of > 48 mg/kg was selected for teratologic effects; a NOAEL of 6 mg/kg was identified for general toxicity findings in dams. In rabbits (15, 30, 60 mg/kg), findings included clinical signs in all groups, and body weight loss (0.0007 kg), reduced food consumption, and increased resorptions at the high dose. No drug-related gross or visceral malformations or variations were observed. Thus, a NOAEL of > 60 mg/kg was selected for teratologic effects; a NOAEL of 30 mg/kg was identified for general toxicity findings in dams.

In the peri- and post-natal study (3, 9, 18 mg/kg), similar clinical signs were noted in high-dose dams of the parent generation as well as reduced food consumption at the high-dose. Survival rate of offspring of high-dose dams was reduced by 7% although 65% of deaths were due to cannibalization. Body weight gain was reduced (8-12%) and a dose-related effect on righting reflex was observed in mid- and high-dose offspring. No significant drug-related effects were observed in the F_2 generation fetuses. Thus, a NOAEL of 3 mg/kg was selected for developmental toxicity in F_1 pups; a NOAEL of > 18 mg/kg was selected for F_1 reproductive

indices and F_2 development; a NOAEL of 9 mg/kg was identified for general toxicity findings in parental dams.

Based upon the results of these studies, the Pregnancy Category for the labeling should be "C" due to adverse fetal effects. This conclusion is in contrast to the sponsor's proposal of a category "B".

Review of Sponsor's Response to Toxicology Concerns (N-000, B-2; 3/20/2000):

Following submission of the Original NDA submission, the sponsor was asked to address an outstanding issue which was outstanding from the previous IND reviews. The sponsor was asked to clarify the term "mineralization" as related to findings in the ovaries of monkeys (i.e., type of minerals) in the 3 month toxicity study (P-6976). A review of the sponsor's response to this issue follows.

The sponsor performed an assay to further characterize the ovarian mineralization in the three month monkey study. Alizarin red stain which reacts with cations and von Kossa stain which reacts with anions were applied to sections of ovary from one monkey in the control group and three monkeys in the high-dose group (72 mg/kg). Material considered to be mineralization by light microscopic examination was positive using the two special stains in high-dose animals while the control animal was positive only with the alizarin red stain. Positive staining of material considered to be mineralization with both alizarin red stain and von Kossa stain suggests that both anions and cations are present. The blue appearance of the material on hemotoxylin and eosin-stained sections and the positivity with both special stains, the mineral is most likely composed of calcium phosphate and/or calcium carbonate In contrast, calcium pyrophosphate and calcium oxalate do not stain with alizarin red. The sponsor further presented background data from control monkeys of numerous previous studies which showed that up to 25-100% of control monkeys displayed minimal to mild ovarian mineralization. Thus, the finding should be considered a normal background change and not a SCH 34117-related effect. The sponsor's response to this issue is acceptable.

OVERALL SUMMARY AND EVALUATION:

SCH 34117 is an active metabolite of loratadine (Claritin) and is an antihistamine acting with greatest potency at the H_1 receptor. Currently, the NDA application 21-165 propose to market SCH 34117 (5 mg oral tablet) for the indication of seasonal allergic rhinitis for patients 12 year or older. In support of the current application the Sponsor has submitted preclinical studies to this NDA and to IND[redacted]including: in vitro and in vivo pharmacology, safety pharmacology, ADME studies in rats, mice, monkeys and rabbits, acute single dose oral and intraperitoneal studies in rats, mice, and monkeys, subacute oral toxicity studies up to 3 months duration in rats and monkeys, reproductive toxicology studies in rats and rabbits, and genetic toxicity studies.

Pharmacodynamics: 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.

Anti-allergic and anti-inflammatory effects of SCH 34117 were demonstrated in numerous *in vitro* and *in vivo* tests. SCH 34117 exhibited 2-3-fold greater oral potency over loratadine in histamine-induced wheal and flare reactions. SCH 34117 inhibited superoxide anion production by PMN, histamine induced activation of endothelial cells, P-selectin expression, release of IL-4 and IL-13, and IL-6 and IL-8, release of histamine, tryptase, LTC_4 and PGD_2, release of RANTES, and attenuated eosinophil chemotaxis and adhesion. Weak inhibitory activity of TNF-α was also observed. *In vivo* functional assays demonstrated that SCH 34117 was more potent than loratadine in inhibiting the guinea pig nasal response to histamine challenge (ED_{50} = 0.9 μg) and in inhibiting cough in ovalbumin sensitized guinea pigs (0.3-1 mg/kg, po). In monkeys, SCH 34117 (5-6.5 mg/kg, po) reduced the bronchospasm and associated increase in airway resistance and decrease in compliance induced by allergen challenge and histamine-induced bronchospasm. Comparable findings in response to histamine challenge were observed with 8 mg/kg loratadine. No effect on decongestion was noted in cats (3 mg/kg, IV). Comments in the proposed label concerning the [redacted] effects of SCH 34117 should be removed since a definitive connection between these properties and the indication of [redacted] has not been demonstrated.

The results of these studies suggest that SCH 34117 may have value as an antihistamine in the treatment of seasonal allergic rhinitis.

Safety Pharmacology: 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 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 6×10^{-6} M as the concentration at which ½ current is blocked (k0.5) was 5×10^{-6} M (k0.5 for loratadine was 8.7×10^{-6}). SCH 34117 had no effect at 10^{-5} M on inward rectifier current (iK1) although the curve was flatter at 3×10^{-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.

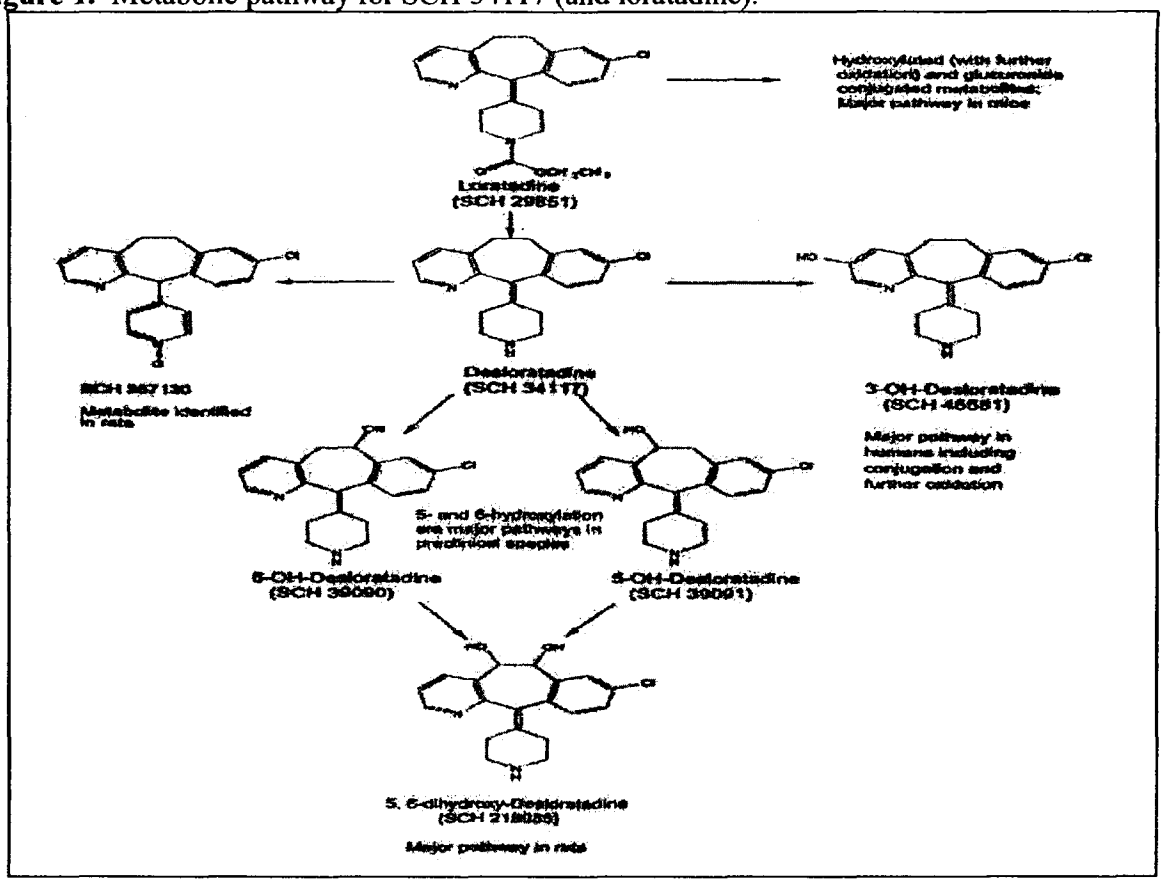
---

[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.

In studies performed under NDA 19-658, loratadine was 10-fold less potent than diphenhydramine in inducing neurological, behavioral, and autonomic effects in mice, dogs, monkeys and in inducing a sedative effect in cats.

Pharmacokinetics: 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. Distribution of 14C-loratadine in pregnant rats demonstrated that radioactivity crossed the placental barrier equally at the post-embryonic period and near-term. Tissue distribution was similar in maternal and fetal tissues with lower levels found in the fetus. Plasma protein binding of SCH 34117 was variable across species as the mouse, rat, monkey and humans demonstrated 94.4%, 90.5%, 85.8% and 85.0% binding, respectively. The comparative species metabolism of SCH 34117 is summarized in Figure 1. SCH 34117 was extensively metabolized in rats, mice and monkeys and the metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products. Metabolism of SCH 34117 occurred through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position was more extensive in humans. Male rats achieved relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. In vitro studies confirmed the results of the in vivo studies and demonstrated that the hydroxylated metabolites are formed in humans although unchanged SCH 34117 was the primary compound detected. The metabolism profile of SCH 34117 is generally similar to that of loratadine with no SCH 34117-specific metabolites formed. Excretion of SCH 34117-related radioactivity was primarily through the feces with a large portion contributed through the bile. Approximately 20-40% was excreted through the urine.

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



Acute Toxicity: Acute, oral and intraperitoneal studies in mice and rats, as well as an oral study in monkeys were submitted to IND [redacted] 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.

Reproduction: 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).

Based upon the results of these studies, the Pregnancy Category for the labeling should be "C" due to adverse fetal effects. This conclusion is in contrast to the sponsor's proposal of "B".

Genotoxicity: Genetic toxicology studies assessing SCH 34117 were submitted to IND [redacted] and included a bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay using human lymphocytes and an *in vivo* mouse bone marrow erythrocyte micronucleus assay. SCH 34117 was negative under the conditions tested in each of the assays. The sponsor also submitted two assays (a bacterial reverse mutation assay and an *in vitro* chromosome aberration assay using human lymphocytes) to the NDA as part of their effort to qualify the presence of two synthesis impurities. These studies also produced negative results.

Carcinogenicity: 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 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). The sponsor should submit the final study report within three years of the NDA approval or study initiation, whichever occurs first.

Special Toxicity: There were no Special Toxicity studies performed in support of IND [redacted] or NDA 21-165. However, two studies were performed in support of loratadine (NDA 19-658) to assess phospholipidosis in rats and dermal sensitization in guinea pigs. Vacuolated peripheral lymphocytes were observed in all rats administered loratadine (240 mg/kg, po, 2 weeks) with no differences noted between Wistar and CD rats. The dermal sensitization test was negative.

Excipients, Degradants and Impurities: As part of the qualification for the drug substance impurities [redacted] the sponsor performed two genotoxicity assays with SCH 34117 with added levels of [redacted] which produced negative findings at impurity levels exceeding those proposed by the sponsor. In a letter dated June 26, 2000, the Sponsor was requested to limit levels of [redacted] impurities to not more than [redacted] % in the drug substance, or provide further qualification for the drug substance impurities (3 month toxicity study using appropriate levels of impurities [redacted] The Sponsor submitted information for qualification and their proposed levels (NMT [redacted] % for [redacted] and NMT [redacted] for [redacted]) were found to be acceptable (see Addendum to Chemistry Consult, dated August 14, 2000).

In conclusion, the pharmacology, pharmacokinetics and toxic potential of SCH 34117 has been evaluated extensively in multiple *in vitro* and *in vivo* studies with SCH 34117 and also with loratadine. Treatment-related disturbances related to systemic phospholipidosis were observed in rats and monkeys following repeat oral dosing in subchronic studies. However, NOAELs observed in all repeat dose studies demonstrated wide safety margins relative to the proposed therapeutic oral dose (5 mg/day; AUC = 56.9 ng.hr/ml) all observed toxicity based on systemic exposures to SCH 34117.

SCH 34117 showed no potential for mutagenic/clastogenic activity in a series of *in vitro* assays and an *in vivo* assay. Loratadine induced hepatic carcinogenicity in male mice and male and female rats. Although the rat study was considered to have adequately assessed the carcinogenic potential of SCH 34117, based upon exposure criterion, the mouse study did not since it did not achieve an appropriate high dose. Thus, the sponsor was informed that a two-year mouse carcinogenicity study with SCH 34117 would be required as a Phase 4 commitment. A study protocol was submitted and a modified dose selection scheme was recommended by the Executive CAC.

The potential of SCH 34117 for reproductive toxicity was characterized in rats and/or rabbits, at high multiples over the proposed clinical dose. Results of these studies revealed effects on male fertility but no teratogenic effects in either species. However, effects on fetal development were evident. Thus, the pregnancy category should be C.

LABELING REVIEW:

To achieve consistency with current Division labeling practices and labeling for Claritin, where appropriate, the following sections should be revised as follows:

DRAFT

2 pages redacted from this section of the approval package consisted of draft labeling

DRAFT

RECOMMENDATIONS

3. The NDA for descarboethoxyloratadine is approvable from a preclinical standpoint pending incorporation of the suggested revisions for the labeling sections entitled: Clinical Pharmacology, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Pregnancy Category, and OVERDOSAGE as indicated above.

4. The sponsor should submit the final study report for the Phase 4 mouse carcinogenicity study within three years of the NDA approval or study initiation, whichever occurs first.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Comment for letter to Sponsor:

The final study report for the Phase 4 mouse carcinogenicity study should be submitted within three years of the NDA approval or study initiation, whichever occurs first.

CC: Original NDA 21-165
HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/D. Nicklas
HFD-570/G. Trout
HFD-570/V. Borders
HFD-570/T.J. McGovern
HFD-540/B. Hill
HFD-590/K. Hastings

Attachments: Exposure ratio calculation table
For NDA Division file only:
IND [redacted] Original Review
IND [redacted] Review #2
IND [redacted] Review #3
IND [redacted] Review #4
Minutes of Senior Pharmacology/Toxicology Policy Team
IND [redacted] Review #5
IND [redacted] Review #6

Studies	DCL AUC	DCL+ DCL metabolites AUC	Animal:human ratio	PB correction	derivation of animal AUC
Human - 5 mg	56.9	711.25			
rat: fertility					
3 mg/kg	1950	8863.64	12	8	3 mos tox study, males
12mg/kg	10440	47454.55	67	44	40% of 30 mg/kg dose in 3 mos study, males
24 mg/kg	31606	143663.64	202	134	Embryo-fetal rat study
rat: embryo fetal					
6 mg/kg	7875	35795.45	50	33	Embryo-fetal rat study
24 mg/kg	31606	143663.64	202	134	Embryo-fetal rat study
48 mg/kg	49238	223809.09	315	208	Embryo-fetal rat study
rat: Seg III					
3 mg/kg	1619	7359.09	10	7	1 month rat tox study
9	10999	49995.45	70	47	30% of 30 mg/kg dose in 1 month tox study
24	29331	133322.73	187	124	80% of 30 mg/kg dose in 1 month tox study
rabbit: embryo-fetal					
60 mg/kg	12987	NA	230		Embryo-fetal rabbit study
Overdosage					
rat-125 mg/kg	21944.5	99747.73	140	93	1-week Pk study at 120 mg/kg; M+F
rat-250 mg/kg	27441	124731.82	175	116	1-week Pk study at 240 mg/kg; M+F
Mouse-250 mg/kg	7115	19229.73	27	10	single oral dose of 6.5 mg/kg; M+F
Mouse-353 mg/kg	10046	27151.35	38	15	
Monkey 250 mg/kg	21422	NA	380		3-month monkey tox study; 18 mg/kg- day 1
Carcinogenicity					
Mouse - 40 mg/kg	1861	5029.73	7	3	28-day dietary study w/lortadine
Rat - 25 mg/kg	7017	31895.45	45	30	28-day dietary study w/lortadine
Rat - 10 mg/kg	1619	7359.09	10	7	28-day dietary study w/lortadine
Species	**DCL/14C ratio**	**Protein binding (%)**			
Mouse	0.37	94.4			
Rat	0.22	90.5			
Human	0.08	85.6			
Monkey	NA	85.8			

HFD-570 : DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Review

IND No. [redacted] **Serial No.** 000 **Submission Date**: 09 MAR 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 22 MAY 98

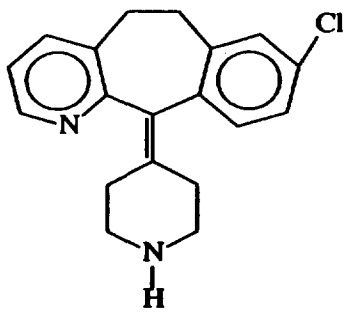
Information to be Conveyed to Sponsor: Yes (✔), No ( )

Sponsor: Schering-Plough Corporation

Drug Names: Descarboethoxyloratadine (DCL) *Code Name:* SCH 34117

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

Structure:



Molecular Weight: 310.82

Formula: $C_{182}H_{310}N_{40}O_{35}$

Related INDs/NDAs/DMFs: NDA 19-658, IND [redacted], IND [redacted] NDA 20-704

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Clinical Formulation:

Components	Amount/tablet type (mg)		
	2.5 mg	5 mg	10 mg
SCH 37114	2.5	5	10
Dibasic calcium phosphate dihydrate USP			
Cellulose microcrystalline NF			
Corn starch NF			
Talc USP			
Blue			
Clear			
Carnauba Wax NF			
White Wax NF			
Total tablet wt.	**106.61**	**106.61**	**106.61**

Route of Administration: Oral (tablet)

Proposed Clinical Protocol:
Objective: Phase II, dose-finding study to examine clinical efficacy and safety of SCH 34117
Dose: 2.5, 5, 7.5, 10, and 20 mg
Frequency: Once per day
Duration of clinical study: 2 weeks
Patient population: Patients with seasonal allergic rhinitis

Previous Clinical Experience: Phase I, rising single-dose study (2.5 - 20 mg) in healthy male volunteers. The follow-up physical examination and vital signs for all patients were normal and no clinically relevant changes were reported.

Previous Review(s), Date(s) and Reviewer(s): None

A Pre-IND meeting was held with the sponsor on 1/12/98 to discuss the potential for bridging to the development program of the SCH 34117 parent compound loratadine (SCH 29851). See the Meeting Minutes for a review of this discussion.

The following table summarizes the studies submitted in the original IND package:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Volume
Pharmacology:		
Comparative anithistaminic activity	Abstract	1.3
Onset of antihistamine activity	D-26677	1.3
Antihistamine activity in monkeys	D-28097	1.3
Anticholinergic actions in guinea pig right atria	P-5950	1.3
Associated muscarinic side-effects	Cited Ref.	1.3
Comparative antihistaminic activity	Cited Ref.	1.3
Comparative effects on cardiac K+ channels	Cited Ref.	1.3
Effects on human cardiac potassium channel Kv1.5	Cited Ref.	1.3
Safety Pharmacology:		
Comparative CNS and cardiovascular profiles	Cited Ref.	1.3
Pharmacokinetics:		
Metabolic profiling in rat, mouse and monkey	D-28407	1.9
Rising single-dose study in healthy human volunteers	I97-248-01	1.17
Acute Toxicology:		
Single-dose oral administration, mice	P-6771	1.15
Single-dose intraperitoneal administration, mice	P-6772	1.15
Single-dose oral administration, rats	P-6769	1.15
Single-dose intraperitoneal administration, rats	P-6770	1.15
Single-dose oral administration, monkeys	P-6808	1.15
Multiple Dose Toxicology:		
14-day oral safety profile, rats	D-18289	1.15
14-day, oral toxicology, rats	P-6526	1.4
14-day, oral toxicology, monkeys	P-6527	1.7
Reproductive Toxicology:		
Pilot Segment I, rats	P-6821	1.16
Pilot Segment II, rats	P-6718	1.16
Pilot Segment II, rabbits	P-6719	1.16
Segment II, rabbits (incomplete submission)	P-6802	1.9
Genetic Toxicology:		
Bacterial reverse mutation assay (Ames test)	P-6609	1.16
Chromosome aberration in human lymphocytes	P-6692	1.16

Studies Not Reviewed in this IND: Four validation studies for the determination of loratadine and SCH 34117 in mouse (Study — Vol. 1.10), rat (P- — Vol. 1.11), cynomolgus monkey (- —, Vol. 1.13) and human plasma (Vol. 1.14) by — The assay for Studies — and — was validated over the range of — ng/ml using a — ml sample. The assay for Study — was validated over the range of — ng/ml using a ml sample. The assay for Study — was validated over the range of — ng/ml using a — ml sample.

Studies Previously Reviewed: None

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

PHARMACOLOGY

Antihistaminic activity: SCH 34117 displayed greater H_1-receptor affinity than the parent drug loratadine, as the two drugs displaced radioligand binding to a cloned H_1 human receptor subtype with IC_{50} values of 51 and 721 nM, respectively[2]. Both compounds were highly selective and showed little affinity for H_2 or H_3. In isolated guinea pig lung tissue, representative of peripheral H_1 receptors, SCH 34117 again showed greater affinity as IC_{50}s of 840 and 3030 nM for SCH 34117 and loratadine, respectively, were reported.

SCH 34117 displayed greater antihistaminic potency than loratadine in various animal models. In guinea pigs, antihistaminic activity of SCH 34117, measured by the inhibition of histamine-induced bronchospasm, showed 4- to 8.5-fold greater potency compared to loratadine (Table 1). Onset of activity was rapid (within 2 minutes) and the peak activity for both compounds was between 30 and 60 minutes. SCH 34117 also displayed a 20-fold greater potency than loratadine (concentrations not provided) in antagonizing histamine-induced contractions of isolated strips of guinea pig ileum[1]. *In vivo*, SCH 34117 also exhibited 2-3 fold greater oral potency over loratadine (doses not provided) in histamine-induced weal and flare reactions[1]. In monkeys, both loratadine (8 mg/kg) and SCH 34117 (6.5 mg/kg), administered by gastric intubation, almost completely inhibited the effects of histamine on airway resistance and compliance. Differences between placebo and treatment groups were significant ($p<0.01$), but treatment groups were not significantly different from each other.

Table 1. Comparative anithistaminic activity of SCH 34117 and loratadine.

Measured Endpoint	SCH 34117	Loratadine
ED_{50}-G. Pig; inhibition of histamine-induced bronchospasm (iv, 2 min)	0.27 mg/kg	2.3 mg/kg
ED_{50}-G. Pig, inhibition of histamine-induced bronchospasm (iv, 60 min)	0.11 mg/kg	0.41 mg/kg

Anticholinergic activity: In studies with cloned human M_1-M_3 receptor subtypes, SCH 34117 expressed a high affinity for the M_1 and M_3 receptor subtypes (IC_{50} of 48 and 125 nM, respectively)[1]. Conversely, a weak affinity for the M_2 receptor (IC_{50} 250-1000 nM) indicated selective anticholinergic activity. Loratadine did not possess any binding activity with muscarinic receptors.

Anticholinergic effects were assessed *in vitro* by decreases in spontaneous right atrial rate induced by acetylcholine before and after loratadine, SCH 34117, astemizole or terfenadine dosing (all at 10 μM; corresponding to a concentration of 3820 ng/ml for loratadine, roughly 1000-fold that existed in the therapeutic setting) using right atria from male [redacted] guinea pigs. The potency of SCH 34117 was comparable to diphenhydramine (Table 2), but significantly less than atropine, as slight anticholinergic activity was noted at 0.1 μM SCH 34117, with significant inhibition noted at 1 and 10 μM (occurring at a concentration 21-fold higher than reported human drug plasma levels). Neither loratadine nor astemizole inhibited responses to acetylcholine.

---

[2] Handley, DA, McCullough, JR, Fang, Y, Wright, SE, and Smith, ER. (1997). Descarboethoxyloratadine, a metabolite of loratadine, is a superior antihistamine (Abstract P164). Annals of Allergy, Asthma and Immunology. 78: 143.

Table 2. In vitro anticholinergic activities in guinea pig right atria.

Substance	pA_2	K_i nM	Relative Potency
Astemizole	NA	NA	NA
Atropine	9.03	1.83	1.000
Diphenhydramine	6.73	298	0.006
Loratadine	NA	NA	NA
SCH 34117	6.81	206	0.009
Terfenadine	NA	NA	NA

NA - Anticholinergic activity not manifested at 10 μM and value could not be determined.
pA_2 - the value represented by the logarithm of 1/[the molar concentration of inhibitor requiring that twice as much agonist be used to elicit the same response as when no inhibitor was present).
K_i - apparent dissociation constant of inhibitor-receptor complex

The muscarinic side-effects of SCH 34117 on pilocarpine-induced salivary secretion (1 mg/kg sc), a functional model for M_3 receptors, topical-induced mydriasis, and oxotremorine hypothermia (measures of M_2 and M_3 receptor response) and OXO-induced tremor (M_3-mediated) were assessed along with fexofenadine, carebastine, terfenadine, loratadine and ebastine in mice[3]. Only SCH 34117 inhibited pilocarpine-induced salivation in mice (IC_{50} = 10.8 mg/kg po and 3.2 mg/kg sc). Loratadine significantly inhibited salivation (24%) only at highest dose (30 mg/kg po). SCH 34117 (10 mg/kg) and atropine (1 mg/kg) also partially inhibited pilocarpine-induced acinar cell degranulation in the submandibular gland, while fexofenadine and carebastine were virtually inactive. SCH 34117 also produced a potent and long lasting (>120 min) mydriasis after topical administration (ED_{50} = 2.7 mg/kg). None of the compounds tested affected oxotremorine hypothermia and OXO-induced tremor.

Cardiac Potassium Channels: The effects of SCH 34117, loratadine and terfenadine on a variety of cardiac K^+ channels were investigated in ventricular myocytes and in *Xenopus* oocytes expressing the *HERG* delayed rectifier[4]. Terfenadine suppressed all of the channels tested (inward rectifier of the rat and guinea pig, I_{K1}; transient outward K^+ current of rat, I_{to}; maintained K^+ current of rat, I_{ped}; and delayed rectifier K^+ channels of guinea pig myocytes, I_{Ks} and I_{Kr}) with greater potency than loratadine and SCH 34117, which were of generally comparable potency (Table 3). Loratadine had little or no suppressive effect on rat ventricular myocyte I_{K1} at doses up to 10 μM; similar results were observed in guinea pig cardiomyocytes. The suppression at 10 μM (15%) was irreversible upon washout. SCH 34117 had similar effects at doses up to 2.5 μM (5% suppression) and irreversibly and non-specifically suppressed I_{K1} at 10 μM. In contrast, the I_{K1} was suppressed by 40% at 1 μM terfenadine. Loratadine had no significant effect on the delayed rectifier channel (I_{Ks}) until doses > 1μM were tested; 25 μM induced a 60% suppression (considered non-specific as this dose also suppressed I_{Ca} and I_{Na}). SCH 34117 was slightly less potent than loratadine and terfenadine was again more potent in suppressing I_{Ks}, inducing a 21% suppression at 0.25 μM. Terfenadine, but not loratadine, almost completely abolished (90%) the

[3] Cardelus, I, Puig, J, Bou, J, Jauregui, J, Fernandez, AG and Palacios, JM. (1997). Xerostomia and mydriasis: Two possible muscarinic peripheral side effects associated with descarboethoxyloratadine, the main metabolite of loratadine. Proc. British Pharmacological Soc.: P149.

[4] Ducic, I, Ko, CM, Shuba, Y, and Morad, M. (1998). Comparative effects of loratadine, and terfenadine on cardiac K^+ channels. J. Cardiovascular Pharmacol. In press.

time dependent component of tail current from I_{Kr} at 1 μM in native guinea pig myocytes. Similar results were obtained with terfenadine (60% suppression) and loratadine (5% suppression) at 1 μM in I_{Kr} expressed in Xenopus oocytes. The outward transient current (I_{to}) was also more potently regulated by terfenadine (40% suppression) than by loratadine (5% or less suppression) at 2.5 μM. SCH 34117 was either ineffective or had a significantly smaller effect in suppressing I_{to} than terfenadine at 1 μM and induced only an 8% suppression at 2.5 μM. The maintained component of I_{to} (I_{ped}) was also more potently suppressed by terfenadine (28% and 40-50% at 1 and 2.5 μM, respectively) than by loratadine (22% at 2.5 μM) or SCH 34117 (15 and 22% at 1 and 2.5 μM, respectively).

Table 3. Relative potency in K^+ channel inhibition.

K+ channel	Relative potency
I_{K1}	terfenadine > loratadine = SCH 34117
I_{Ks}	terfenadine > loratadine > SCH 34117
I_{Kr}	terfenadine > loratadine
I_{to}	terfenadine > loratadine = SCH 34117
I_{ped}	terfenadine > loratadine = SCH 34117

In a second study cited by the sponsor, the effects of SCH 34117 on cardiac K^+ channel (hKv1.5) cloned from human ventricle and stably expressed in a mouse cell line (Ltk-) were assessed[5]. SCH 34117 blocked hKv1.5 channels, which generate the ultra-rapid delayed outward K^+ current in human atria, in a concentration-, voltage-, and time-dependent manner. SCH 34117 (1 to 100 μM) inhibited hKv1.5 current with an apparent affinity constant (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. The blockade by SCH 34117 increased over the voltage range, indicating that SCH 34117 binds preferentially to the open state of the channel. In addition, a concentration of 20 μM increased the time constant of deactivation of tail currents, thus inducing a "crossover" phenomenon.

Summary of Pharmacology

SCH 34117 displayed a 14-fold greater affinity for the H_1-receptor than loratadine and was up to 20-fold more potent than loratadine in antihistaminic activity in guinea pigs. Antihistaminic potency on airway effects was comparable in monkeys. SCH 34117 also showed an affinity for M_1- and M_3-receptors, but not for M_2-recptors. In contrast, loratadine displayed no affinity for muscarinic receptors. SCH 34117 dose-dependently expressed anticholinergic activity by decreasing the spontaneous right atrial rate in male Hartley guinea pigs (0.1 to 10 μM) and showed similar potency to diphenhydramine, but was significantly less potent than atropine. In addition, SCH 34117 was more potent than loratadine in inhibiting pilocarpine-induced salivation in mice (IC_{50} = 10.8 mg/kg po and 3.2 mg/kg sc; loratadine significantly inhibited salivation (24%)

[5] Caballero, R, Delpon, E, Valenzuela, C, Longobardo, M, Franqueza, L, and Tamargo, J. (1997). Effect of descarboethoxyloratadine, the major metabolite of loratadine, on the human cardiac potassium channel Kv1.5. Br. J. Pharmacol., 122, 796-798.

only at highest dose of 30 mg/kg po). SCH 34117 was also more potent than fexofenadine and carebastine, but less potent than atropine in inhibiting pilocarpine-induced acinar cell degranulation in the submandibular gland. SCH 34117 also produced a potent and long lasting (>120 min) mydriasis after topical administration (ED_{50} = 2.7 mg/kg), but did not affect oxotremorine hypothermia and OXO-induced tremor. Both SCH 34117 and loratadine were significantly less potent than terfenadine in inhibiting rat and guinea pig cardiac K^+ channels. 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).

SAFETY PHARMACOLOGY

Cardiovascular effects: Loratadine (30 and 100 mg/kg, iv) did not alter BP, HR, QTc interval, PR interval, QRS interval or the normal ECG wave form in the guinea pig at plasma levels (27.8 - 61 μg/ml) at least 5500X greater than plasma levels in man[6]. Although SCH 34117 was not administered directly, the resulting SCH 34117 concentrations (1.46 μg/ml) were 370X greater than the SCH 34117 C_{max} in man after a single oral dose of 10 mg loratadine. Promethazine (5 mg/kg, iv) was also devoid of adverse cardiovascular and ECG effects. In contrast, terfenadine (10 mg/kg, iv) induced hypotension, bradycardia and prolongation in the QTc interval up to 500 ms and produced a torsades de pointes-like syndrome. Similarly, quinidine (50 mg/kg, iv) produced hypotension, bradycardia and QTc prolongation. Diphenhydramine (20 mg/kg, iv) also produced significant cardiovascular and ECG effects (bradycardia, hypotension, and increased the PR and QRS interval), but did not prolong the QTc interval or torsades-like arrhythmias.

PHARMACOKINETICS AND TOXICOKINETICS

Single/Multiple Dose Pharmacokinetics:

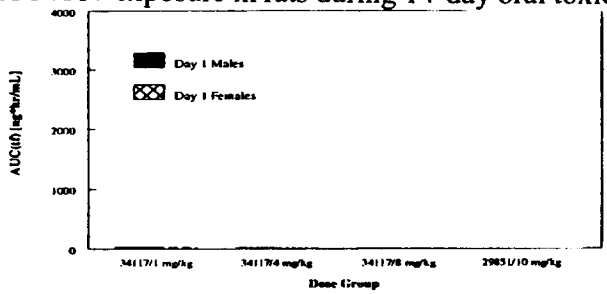
The toxicokinetics of two 14-day oral toxicity studies were submitted and are summarized briefly in Figures 1 (rat) and 2 (monkey), and in greater detail in the Toxicology section of this review. Exposures to SCH 34117 increased supra-proportionally with dose in the rat following oral administration (1-8 mg/kg/day) on Day 1 (Figure 1) and were generally greater on Day 10 compared to Day 1 at doses > 1 mg/kg/d, indicating the potential for drug accumulation. In addition, exposure levels in females were consistently greater (1.6- to 4.9-fold) than in males at comparable doses and exposure durations. Maximum plasma concentrations also increased supra-proportionally, but not to the extent of AUC. In contrast, SCH 34117 exposure in male monkeys increased sub-proportionally with dose following oral administration on Day 1 (Figure 2). In female monkeys, although exposures increased proportionally at the mid-dose and supra-proportionally at the high-dose, exposure levels in females at the two lower doses, were 2- to 5-

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

fold less than those in males at comparable doses and exposure durations. Exposures were not significantly different between Days 1 and 14 at the two lower SCH 34117 doses, although indications of drug accumulation were present at the high dose as exposures increased 1.4- to 1.8-fold. Maximum plasma concentrations also increased sub-proportionally compared to dose. Exposures increased proportionally in human male volunteers administered single doses of SCH 34117 (Table 4) and, similar to rats and monkeys, drug accumulation (of SCH 34117) was observed following multiple doses of loratadine (Table 5). Mean T_{max} was achieved between 2.5-12 hours in the rat following SCH 34117 administration on Day 1, increasing with increasing dose, and at 2.5 hours at Day 10. A similar mean T_{max} was achieved in the monkey (2.5-8 hours) following SCH 34117 administration and in humans administered single doses (2.5-20 mg; 1.7-3.6 hours). The terminal phase half-life of SCH 34117 in the rat, monkey and human was approximately 2-4 hours, 7-12 hours and 24.6 hours (single 20 mg dose), respectively.

Administration of 10 mg/kg loratadine (equimolar to 8 mg/kg/d SCH 34117) in the rat resulted in greater exposures to SCH 34117 than to the parent compound (2.3- to 14.7-fold). These exposures were, however, less than those observed following administration of high-dose SCH 34117 with the exception of males at Day 1. SCH 34117 exposure was again greater in female rats and greater on Day 10 than on Day 1. Administration of 8 mg/kg/d loratadine (equimolar to 6.5 mg/kg/d SCH 34117) in the monkey also resulted in greater exposures to SCH 34117 than to the parent compound (6.7- and 7.4-fold in females and males, respectively) on Day 1, and increased to 13- and 36-fold, respectively by Day 14. Exposures were less than those observed following administration of high-dose SCH 34117 (65-80%). Similar to administration of SCH 34117, SCH 34117 exposure was greater in males (~1.6-fold) and was greater on Day 14 than on Day 1 (1.3-fold).

Figure 1. SCH 34117 exposure in rats during 14-day oral toxicity study.



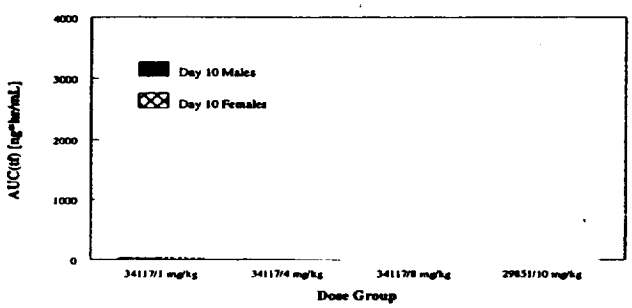
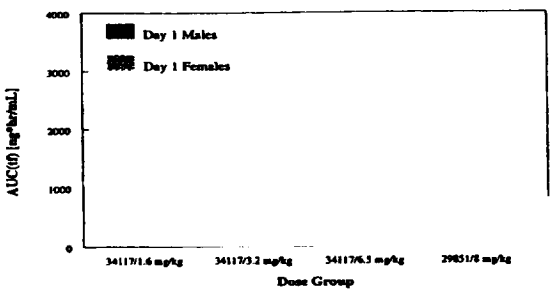


Figure 2. SCH 34117 exposure in monkeys during 14-day oral toxicity study.



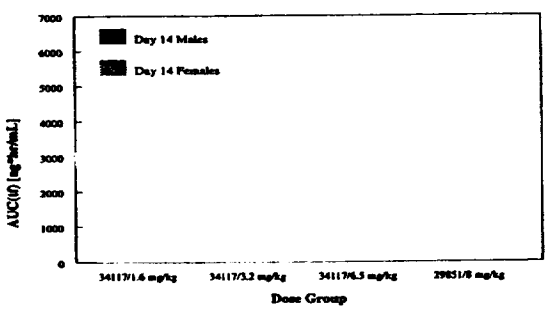


Table 4. Single dose toxicokinetics of SCH 34117 in humans.

SCH 34117 (mg)	$t_{½}$ (hr)	T_{max} (hr)	C_{max} (ng/ml)	AUC(0-t hr)[a] (ng.h/ml)
2.5		3.55	0.80	9.77
5		1.7	1.67	20.7
10		2.15	4.26	70.4
20	24.6	2.20	8.36	158

[a] AUC(0-t hr) values calculated using the mean concentration data. t = 78 hr.

Table 5. Plasma SCH 34117 concentrations in humans following single and multiple dose administrations of loratadine.

Loratadine (mg)	$t_{½}$ (hr)	T_{max} (hr)	AUC(0-t hr)[a] (ng.h/ml)
Single dose			
10	15.6	1.7	29.1
	24.9	2.0	50.9
Multiple dose			
10		4.6	73.4
		2.7	48.4
		3.0	97
		3.0	112
		2.9	93.5

[a] AUC(0-t hr) values calculated using the mean concentration data. t = 24-84 hr.

Absorption: The blood and plasma concentration of administered radioactivity in rats and mice and plasma and bile concentrations in a monkey following single oral doses of SCH 34117 or loratadine were measured by liquid scintillation spectrometry. Radioactivity was equally distributed between blood and plasma regardless of the administered compound (2-9 mg/kg SCH 34117: 0.30-0.66 µg.eq/g; 8-9 mg/kg loratadine: 0.43-1.17 µg.eq/g) in rats and mice. In monkeys, the administered doses were well absorbed as concentrations of radioactivity were greater in the bile (13.7-150 µg.eq/g) than in plasma (0.26-7.28 µg.eq/g).

Plasma Protein Binding: Plasma protein binding of SCH 34117 was comparable between rats, monkeys and humans (70-76%; See NDA 19-658 original Summary, dated 10/30/87). Binding of loratadine was significantly greater (97-99%)

Metabolism: The metabolism of loratadine and SCH 34117 is summarized in Figure 3. Loratadine is primarily metabolized to SCH 34117 through the removal of the carboethoxy group. This compound is further metabolized and the metabolites are excreted unchanged, as glucuronides or as further oxidized and conjugated products. In a pilot study to obtain comparative metabolism data on radiolabeled SCH 34117 and loratadine (both compounds at least 98% radiochemically pure) using [redacted] male rats, mice and a monkey received single doses of ^{14}C-loratadine, ^{14}C-SCH 34117 or SCH 34117 (target doses of 8 mg loratadine/kg and 6.5 mg SCH 34117/kg). Table 6 shows that the results are comparable to

the original metabolic profile reported for loratadine and that no metabolites are specific to SCH 34117 administration. However, metabolites specific to loratadine were detected in the pooled plasma and bile of male mice (monohydroxy loratadine glucuronide, monoketo-monohydroxy loratadine, monohydroxy loratadine glucuronide). In addition, previously unreported metabolites were observed in rat urine and plasma following dosing with SCH 34117 and loratadine (unknown metabolite RM1: m/z 323; 5,6-dihydroxy-SCH 34117, and three unknown metabolites RM3: m/z 339). Also, a significant portion of loratadine was hydroxylated directly without first being metabolized to SCH 34117 in the mouse.

Figure 3: Proposed metabolic pathway of Loratadine/SCH 34117.

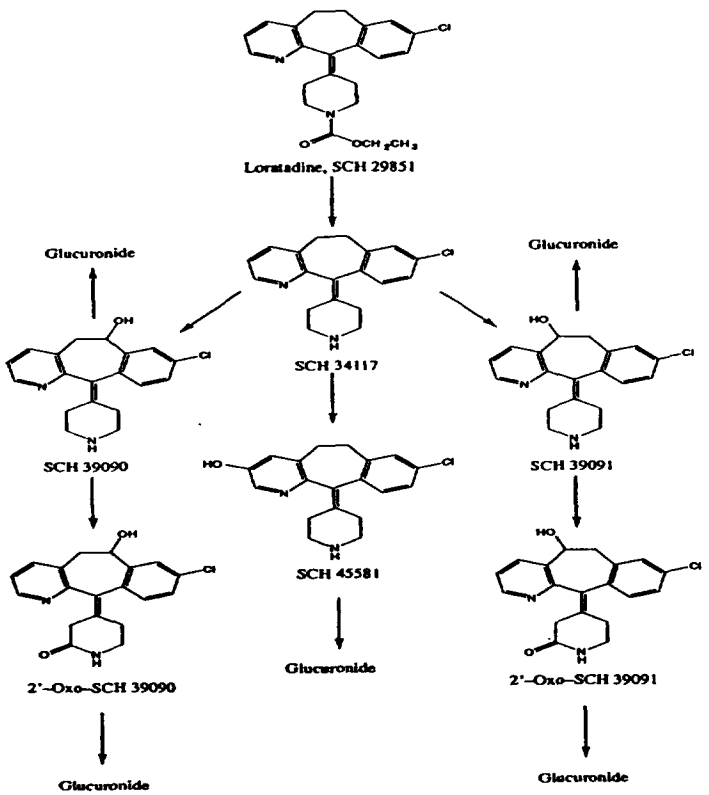


Table 6. Relative abundance of metabolites following oral, single dose administrations.

Matrix	Metabolite	Administered Compound SCH 34117			// SCH 29851		
		Rat	Mouse	Monkey	Rat	Mouse	Monkey
Plasma	SCH 34117	+++	+++	+++	+++	+	+
	loratadine						+
	RM1 (m/z 323; unknown)	+++			+++		
	5-OH SCH 34117	+	+	+	++	++	++
	6-OH SCH 34117	+	+	++	++	++	+
	monohydroxy SCH 29851 glucuronide					+++	
	monoketo-monohydroxy SCH 29851					+	
	MM5 (m/z 339; unknown)		++			+	
	3-OH SCH 34117-glucuronide			+			++
	5-OH SCH 34117-glucuronide			++			+++
	6-OH SCH 34117-glucuronide			+			+
	monohydroxy SCH 34117 glucuronide			+			+
Urine	SCH 34117	+	++	+	+	+	+
	RM3 (m/z 339; 3 unknowns)	++			++		+
	5-OH SCH 34117	+++	+++	++	+++	+++	+
	6-OH SCH 34117	+++	++	++	+++	++	
	5,6-dihydroxy-SCH 34117	+++			++		
	monoketo-SCH 29851				+		
	3-OH SCH 34117-glucuronide			+			+
	5-OH SCH 34117-glucuronide			+++			+++
	6-OH SCH 34117-glucuronide			+			+
	monohydroxy SCH 34117 glucuronide			+			+
Bile	SCH 34117	+	+++		+	+	
	5-OH SCH 34117	+++	++	++	+++	+	++
	6-OH SCH 34117	+++	+	++	+++	+	++
	3-OH SCH 34117-glucuronide (rat)	++			+++		
	monohydroxy SCH 29851 glucuronide					+	
	3-OH SCH 34117-glucuronide (mouse)		+			+	
	dihydroxy-SCH 29851 monogluc.					+++	
	5-OH SCH 34117-glucuronide			+			+
	6-OH SCH 34117-glucuronide			+			+

Excretion: Following single oral doses of SCH 34117 or loratadine, radioactivity was excreted primarily in the feces of rats (71-79%) and mice (39-54%), although a significant portion was excreted in the urine (25-36% in rats; 20-41% in mice). In monkeys, radioactivity was detected primarily in the bile (46-58%) and urine (40-48%), with a small portion excreted in the feces (8-9%) after 48 hours. Previous studies in the development of loratadine are in agreement with these results as excretion in rats, mice, rabbits and monkeys was primarily through the feces, although a significant portion was also excreted in the urine (See Original NDA 19-658 Review, dated 10/30/1987).

Summary of Pharmacokinetics and Toxicokinetics

The comparative pharmacokinetics of SCH 34117 are summarized in Table 7. Following multiple-dose oral administration (14 day, 1-8 mg/kg in rats, 1.6-6.5 mg/kg in monkeys), plasma levels and systemic exposures to SCH 34117 increased supra-proportionally with dose in rats and female monkeys, and proportionally in male monkeys. Exposures were generally greater in female rats than in males, and greater in male monkeys than in females. Drug accumulation was evident in both species. At similar doses, exposures were greater in monkeys. Maximum plasma concentrations in rats were achieved within 2.5-12 hours on Day 1, increasing with increasing dose, and within 2.5 hours on Day 10. In the monkey, mean T_{max} was achieved within 2.5-8 hours. The terminal phase half-life of SCH 34117 was ~ 2-4 hours in the rat, increasing to ~ 7.5-12 hours in monkeys and 24.6 hours in humans. Administration of 10 or 8 mg/kg/d loratadine in the rat and monkey, respectively, resulted in greater exposures to SCH 34117 than to the parent compound. Whether administered as SCH 34117 or loratadine, radioactivity was equally distributed between blood and plasma in rats and mice, and plasma protein binding is comparable among rats, monkeys and humans (70-76%). The metabolism of SCH 34117 is comparable to its parent, loratadine, which is primarily metabolized to SCH 34117 via removal of the carboethoxy group. This compound is further metabolized and the metabolites are excreted unchanged, as glucuronides or as further oxidized and conjugated products. However, metabolites specific to loratadine were detected in the pooled plasma and bile of male mice (monohydroxy SCH 29851 glucuronide, monoketo-monohydroxy SCH 29851, monohydroxy SCH 29851 glucuronide). In addition, previously unreported metabolites were detected in rat urine and plasma following dosing with SCH 34117 and loratadine. Also, a significant portion of loratadine was hydroxylated directly without first being metabolized to SCH 34117 in mice. Fecal excretion is the primary route of elimination, although a significant portion is also excreted in the urine following oral administration.

Table 7. Comparative pharmacokinetics of SCH 34117.

	Rat	Mouse	Monkey	Human
Single dose				
AUC (ng.h/ml)				
-8 mg/kg	2027			
-6.5 mg/kg			3172	
-20 mg				158
$T_{1/2}$ (hr)				
-8 mg/kg	3.3-3.7			
-6.5 mg/kg			7.8	
-20 mg				24.6
T_{max} (hr)				
-8 mg/kg	12			
-6.5 mg/kg			2.5	
-20 mg				2.2
Protein binding (%)	70		71	77
Excretion (oral dose)				
-Urine (0-48 hr)	35.6	40.8	39.8	
-Feces (0-48 hr)	78.9	37.8	8.24	
-Bile (48 hr)			58.4	

TOXICOLOGY

ACUTE TOXICITY:

The following single-dose studies in mice, rats and monkeys are summarized in Table 8, page 16.

Mouse, Acute Oral Toxicity

Study No.: P-6771 *Report No.*: 97238 *Volume*: 1.15

Study Dates:	Starting date 10/22/97; report issued 2/13/98
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139)
Concentration:	10-20 mg SCH 34117/ml
Dose Volume:	5-25 ml/kg
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

Mouse, Acute Intraperitoneal Toxicity

Study No.: P-6772 *Report No.*: 97239 *Volume:* 1.15

Study Dates:	Starting date 10/22/97; report issued 2/13/98
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139) in 0.4% (w/v) aqueous methylcellulose
Concentration:	10-20 mg/ml
Dose Volume:	2.5-25 ml/kg
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

Rat, Acute Oral Toxicity

Study No.: P-6769 *Report No.*: 97236 *Volume:* 1.15

Study Dates:	Starting date 10/20/97; report issued 2/13/98
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139) in 0.4% (w/v) aqueous methylcellulose
Concentration:	50-200 mg/ml
Dose Volume:	1-10 ml/kg
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

Rat, Acute Intraperitoneal Toxicity

Study No.: P-6770 *Report No.*: 97237 *Volume:* 1.15

Study Dates:	Starting date 10/20/97; report issued 2/13/98
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139) in 0.4% (w/v) aqueous methylcellulose
Concentration:	50 mg/ml
Dose Volume:	0.5-10 ml/kg
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

Monkey, Acute Rising Dose Oral Toxicity

Study No.: P-6808 *Report No.*: 97240 *Volume:* 1.15

Study Dates:	Starting date 11/5/97; report issued 2/12/98
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-34117-X-02 RA) in 0.4% (w/v) aqueous methylcellulose
Concentration:	2.35-50 mg/ml
Dose Volume:	3.75-5 ml/kg
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

Table 8. Acute toxicity of administered SCH 34117 in mice, rats and monkeys.

Species/ Route	Study # and Dose (mg/kg)	n	Mortality	Occurrence	LD_{50} (mg/kg)	Other findings
Mice	**P-6771**				M: 353	ataxia, convulsions, gasping, hypoactivity,
	50	10			F: 353	tremors, cool to touch, no feces, pallor,
Oral	125	10				prostration, urogenital staining (M),
	250	10				salivation (1 F); (500 mg/kg)
	500	10	10	w/in 1 hr		
	P-6772				M: 49	
	25	10			F: 46	hypoactivity (≥ 50), ataxia, convulsions,
	50	10	3M, 4F	Day 2 to 4		tremors, prostration, dehydration (≥ 125),
IP	125	10	10	2 min to 5 d		gasping (≥ 250), cool to touch (1 each; 50,
	250	10	10	w/in 24 h		250, 500), pallor (1 M; 125), urogenital
	500	10	10	w/in 24 h		staining (M; 50 and 125), inguinal swelling (1M; 50)
Rats	**P-6769**				M: 616	cool to touch, hypoactivity, dehydration and
	50	10			F: 549	urogenital staining (≥ 250), vocalizations,
	125	10				convulsions, tremors, salivation and
Oral	250	10	1M	Day 5		chromodacryorrhea (2000), scant feces (250
	500	10	1M, 1F	24 hr to 2 d		& 500), no feces (250 & 2000),
	2000	10	10	w/in 15 min		chromorhinorhea (≥ 500), gasping & abdominal distension (1M; 250)
						BW: Males: ↓ Day 8; ↑ Day 15 (50-500)
						Females: ↓ Day 8 and 15 (50-500)
	P-6770				M: 178	
	25	10			F: 68	inguinal swelling (≥ 25), ataxia, cool to touch
	50	10	3F	5, 9, or 14 d		and hypoactivity (≥ 50), abdominal
IP	125	10	3M; 4F	w/in 24 h		distension, no/scant feces and urogenital
	250	10	3M; 4F	w/in 24 h		staining (50, 125 & 500), dehydration (50,
	500	10	4M; 5F	15 min - 7 d		250 & 500), convulsions (125-500), tremors & ocular discharge (125 & 250), gasping (125 & 500), prostration (250 & 500), chromodacryorrhea & hyperactivity (500), ↑ respiration & scabs (250), chromorhinorhea (50 & 500)
						BW: ↓ Day 8; ↑ Day 15 (M:50-250; F:50)
Monkey	**P-6808**		None			emesis in males (≥ 23.5) and females (≥
	11.75	2				93.75), diarrhea (1M: 93.75; 1F: 250),
Oral	23.5	2				**Food consumption:** ↓ Day 2 (M: 46.9 &
	46.9	2				93.75)
	93.75	2				
	125	2				
	250	2				

In mice, the maximum non-lethal doses were 250 mg/kg (oral) and 25 mg/kg (ip). The minimum lethal doses were 500 mg/kg (oral) and 50 mg/kg (ip). In rats, the maximum non-lethal doses were 125 mg/kg (oral) and 25 mg/kg (ip). The minimum lethal doses were 250 mg/kg (oral) and 50 mg/kg (ip). In monkeys, the maximum oral dose of 250 mg/kg did not induce lethality. However, emesis, diarrhea and reduced food consumption were observed in some animals administered ≥ 23.5, 93.75 and 46.9 mg/kg, respectively.

MULTIPLE-DOSE TOXICITY:

Rat, 14-day Oral Toxicity

Report No.: P-6526 *Study No.*: 97014 *Volume*: 1.4

Study Dates:	Starting date 2/3/97; report issued 12/23/97
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration:	0.2-1.6 mg SCH 34117/ml; 2 mg loratadine/ml
Dose Volume:	5 ml/kg/day
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

Methods: CRL:CD® (SD)BR VAF/Plus® rats (6 weeks old; males: 186.8-239.3 g toxicity study, 172.3-245.6 plasma analysis; females: 138.6-183.6 g toxicity study, 133.8-186.1 plasma analysis) were assigned to the following treatment groups:

Dose (mg/kg/day):	0	1	4	8	**10 mg loratadine/kg/day**
No./sex toxicity study	10	10	10	10	10
No/sex plasma analysis	6	18	18	18	18

Rats received daily oral doses of vehicle, test drug or comparative dose of loratadine (equimolar to high dose of SCH 34117) for 14 to 16 days. The following observations were made:

Clinical observation	daily
Body weight	weekly
Food consumption	weekly
Water consumption	not assessed
Ophthalmoscopy	once pretest and during Week 2
EKG	not performed
Hematology	Days 7, 8 and 9
Clinical chemistry	Days 7, 8 and 9
Urinalysis	Days 7, 8 and 9
Enzyme induction	livers from control, comparative control (loratadine), and SCH 34117 mid- and high-dose groups (n=3/group) assayed for protein content, cytochrome P-450 content, 7-pentoxyresorufin O-dealkylase (PROD) activity, and 7-ethoxyresorufin O-deethylase (EROD) activity
Organ weights	at sacrifice; (for specific organs see Addendum, page 31)
Gross pathology	at sacrifice
Histopathology	at sacrifice; organs/tissues from vehicle control, comparative control and high-dose SCH 34117, rats dying prior to scheduled necropsy and all gross lesions (for specific tissues/organs see Addendum, page 31)
Toxicokinetics	Day 1 and 10; samples collected at 20 and 40 min and 1, 1.5, 2.5, 4, 8, 12 and 24 hours post-dose on Days 1 and 10 (n=3 rats/sex/timepoint); measured using [redacted] assay ([redacted] LOQ = [redacted] ng/ml)

Results: Results are summarized in tables 9-12.

Mortality: The deaths of one low-dose male and one high-dose female, found dead on Days 9 and 8, respectively, following blood sample collection, were attributed to extravascular blood loss. In addition, six plasma analysis subgroup rats (2 males and 3 females from the loratadine group and 1 male from the mid-dose SCH 34117 group) were found dead after bleeding samples were obtained on Days 1 and 10. These deaths were also attributed to extravascular blood loss and/or trauma of jugular bleeding.

Clinical Observations: No treatment-related effects.

Body Weight: No toxicologically significant treatment-related effects due to SCH 34117. However, mean body weight gains for the loratadine-treated animals were slightly reduced (14-16%) compared to vehicle controls (Table 9).

Food Intake: Food consumption (reported as g/kg/day) was significantly increased (13.2%) only in high-dose males during Week 2 (Table 9).

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: SCH 34117 induced a slight, but dose-dependent, increase in AP (6-27%) in treated males, in addition to a 20% increase in ALT in high-dose males (Table 9). Loratadine also increased levels of ALT (26%), AST (64%), AP (9%) and total bilirubin (48%).

Table 9. Clinical observations and chemistry findings in rats.

	Males					Females				
Dose (mg /kg/d)	0	1	4	8	Lorat.	0	1	4	8	Lorat.
Body Weight Gain										
%Δ vs control group		↓4	↓4	no Δ	↓14		↓5.8	↓11	↓6.7	↓15.6
Food Consump. (g/day)										
%Δ vs control group		no Δ	no Δ	↑7	↑14		↓2	↑4	↑2	↑2
Clinical Chemistry										
AP										
%Δ vs control group		↑6	↑9	↑27	↑9		↑1	↑7	↑3	↓5
ALT										
%Δ vs control group		↑6	↑4	↑20	↑26		↑2	↑9	↑2	↓3
AST										
%Δ vs control group		↑6	↓1	↑8	↑64		↑4	↓3	↓10	↓13
Total billrubin										
%Δ vs control group		↑22	↑9	↑6	↑48		↑2	↑13	↓5	↓4

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: No toxicologically significant treatment-related effects.

Enzyme Induction: Administration of mid- or high-dose SCH 34117 did not significantly increase drug metabolizing enzyme activity due to high inter-animal variability, although "a trend suggestive of slight induction" was noted (Table 10; PROD activity was increased by 113 and 183% in males and 31 and 46% in females, at the mid- and high-dose, respectively). Administration of loratadine significantly increased PROD (131 and 519%, females and males, respectively) and EROD (49%; males only) activities. Neither compound altered absolute or relative liver weight, microsomal protein or cytochrome P-450 content.

Table 10. Enzyme induction in rats.

	Males					Females				
Dose (mg/kg/d)	0	1	4	8	Lorat.	0	1	4	8	Lorat.
Enzyme Induction										
PROD (pmol/min/mg mic. prot.)	47		100	133	[redacted]	13		17	19	[redacted]
EROD (pmol/min/g liver)	1791		2509	2357	[redacted]	1673		1691	1874	1866

Shaded areas indicate a significant difference from vehicle controls.

Gross Pathology: No toxicologically significant treatment-related effects were observed.

Histopathology: No toxicologically significant treatment-related effects were observed. However, various findings with unclear toxicological significance and generally low severity were reported (Table 11). The sponsor did not assess these findings in the lower-dose groups.

Table 11. Histopathological changes following 14-day SCH 34117 administration in rats.

	Males				Females				
Dose (mg/kg/d)	0	4	8	Lorat.	0	1	4	8	Lorat.
Histology* n=	**10**	**2**	**10**	**10**	**10**	**1**	**1**	**9**	**10**
Eye - retinal folds	2(1.5)		3(1)	1(1)	1(1)			2(1)	0
Brain									
-pineal cytopl. vacuolat.	0		1(3)	0	0			0	0
Thymus - thrombosis	0		1(NR)	0	0			0	0
Liver - focal necrosis	1		0	0	0		1(2)	1(1)	2(1)
Kidneys - hydronephrosis	0	1(3)	1(3)	0	0	1(4)		0	0
Mandib. Lymph Nodes									
- lymphoid hyperplasia	0		1(1)	0	0			0	0
Epididymes - mono. cell infil.	2(1)		3(1)	5(1)					
Uterus - eosino. infil.					4(1)			5(1)	2(1)

* Incidence(severity). Severity based upon 0-4 scale in which 0, 1, 2, 3, 4 indicate none, minimal, mild, moderate or severe, respectively. NR - not reported.

Toxicokinetics: Table 12 summarizes the results of the toxicokinetic analysis in which plasma levels were measured using [redacted]. Exposures to SCH 34117 increased supra-proportionally with dose following oral administration on Day 1 as 4- and 8-fold increases in dose resulted in 5.4- to 9.9-fold and 22.8- to 34.7-fold increases, respectively, in exposure. Exposures were generally greater at Day 10 compared to Day 1 at doses > 1 mg/kg/d, indicating the

potential for drug accumulation, and 4- and 8-fold increases in dose resulted in 23- to 35-fold and 50- to 61-fold increases, respectively, in exposure. In addition, exposure levels in females were consistently greater (1.6- to 4.9-fold) than in males. Maximum plasma concentrations also increased supra-proportionally compared to dose, but not to the extent of AUC. Mean T_{max} was achieved between 2.5-12 hours on Day 1, increasing with increasing dose, and at 2.5 hours on Day 10. The terminal phase half-life was approximately 2-4 hours following administration.

Administration of 10 mg/kg/d loratadine (equimolar to 8 mg/kg/d SCH 34117) resulted in greater exposures to SCH 34117 than to the parent compound (2.3- to 14.7-fold). Exposures were generally less than those observed following administration of high-dose SCH 34117 (10-57%) with the exception of males at Day 1 (increased by 17%). Similar to administration of SCH 34117, SCH 34117 exposure was greater in females (1.8- to 2.1-fold) and was greater on Day 10 than on Day 1 (1.6- to 1.8-fold).

Table 12. 14-day toxicokinetics of SCH 34117 and loratadine in the rat.

Dose (mg/kg/d)	Analyte	Day	$t_{½}$ (hr)	T_{max} (hr)	C_{max} (ng/ml)	AUC(tf)[a] (ng.h/ml) Males	Females	Avg.
1 (SCH 34117)	SCH 34117	1	3.5	2.5	4.5	30.7	78.7	58.3
		10	NA	2.5	6.8	30.1	60.4	54.3
4 (SCH 34117)	SCH 34117	1	2.6	8	39.1	166	781	474
		10	3.5	2.5	58.9	359	1056	708
8 (SCH 34117)	SCH 34117	1	3.3 (M)	12	138	700	3425	2027
		10	3.7 (M)	2.5	154	1882	2976	2421
10 (Loratadine)	SCH 34117	1	4.6	1	103	820	1497	1158
		10	4.3	2.5	174	1296	2686	1789
	Loratadine	1	2.5	0.7	92.8	351	252	301
		10	2.3	1	89.2	285	183	245

[a] AUC(tf) values calculated using the mean concentration data (generally 3 males and 3 females at each timepoint).
M: data available for males only.

The high-dose of 8 mg SCH 34117/kg/day was selected as the NOAEL for this study. Target organs of toxicity could not be identified at the doses selected for this study.

Rat, 14-day Oral Toxicity

Report No.: D18289 *Study No.*: SN 83111 *Volume*: 1.15

Study Dates:	Starting date not provided; report issued 6/29/84
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch# 16378-106-1; purity not provided) in 0.4% (w/v) aqueous methylcellulose
Concentration:	mg SCH 34117/ml
Dose Volume:	5 ml/kg/day
GLP:	The study was unaudited.
QA report:	No.

Methods: [redacted] rats were assigned to the following treatment groups:

Dose (mg/kg/day)	0	15	60	240
No./sex toxicity study	13	13	13	13
No./sex plasma analysis, Day 1	4	4	4	4
No./sex plasma analysis, Day 13	4	4	4	4

Each rat received a daily dose of vehicle or test drug by gastric intubation for 14 days. The following observations were made:

Clinical observation . . . daily
Body weight . . . . . weekly
Food consumption . . . . weekly
Water consumption . . . not assessed
Ophthalmoscopy . . . . . predose and week 2
Hematology . . . . . Days 7 and 14; control, low- and mid-dose animals (high-dose animals not tested due to high mortality). Endpoints included hematocrit, hemoglobin, erythrocyte count, mean corpuscular hemoglobin concentration, total and differential leukocyte counts, and platelet counts.
Clinical chemistry . . . . Days 7 and 14; control, low- and mid-dose animals (high-dose animals not tested due to high mortality). Endpoints included glucose, urea nitrogen, glutamic-pyruvic transaminase (GPT), glutamic oxaloacetate transaminase (GOT), and alkaline phosphatase.
Urinalysis . . . . . not performed
Enzyme induction . . . . not performed
Organ weights . . . . . at sacrifice; limited to kidneys, livers and lungs
Gross pathology . . . . . at sacrifice
Histopathology . . . . . at sacrifice; limited to kidneys, livers, lungs and pancreas, in addition to organs with gross lesions
Toxicokinetics . . . . . Day 1 from 4 rats/sex/ treatment group at 1, 3 and 6 hours; Day 13 from 4 rats/sex/group in the low- and mid-dose groups at 1, 3 and 6 hours

Results: Results are summarized in tables 13-16.

Mortality: All high-dose rats were either found dead or sacrificed in anticipation of death on Days 2 through 6.

Clinical Observations: No treatment-related effects were observed in controls, low- or mid-dose animals. High-dose animals exhibited chromorhinorrhea, slow righting-reflex, chromodacryorrhea, and distended abdomen and salivation (females only) between Days 2 through 6.

Body Weight: A reduction in body weight gain (13-26%) was observed in all but one high-dose animal by Day 6. Mid-dose males and females also exhibited a ~12 and 14% reduction in body weight, respectively, compared to controls after 2 weeks. Low-dose females displayed a ~ 6% reduction in body weight compared to controls.

Food Intake: Mean food consumption was reduced (~65%) in high-dose animals by Day 6. Food consumption was also significantly lower for mid-dose males at week 1 (13%), and mid-dose females at week 1 and 2 (21 and 20%, respectively).

Ophthalmoscopy: The sponsor reported that no toxicologically significant treatment-related effects were observed, however, no data was included to support conclusion.

Hematology: Reduced leukocyte counts were observed in high dose rats sacrificed on day 5 and 6 (Table 13). The incidence of lymphocytic cytoplasmic vacuoles was reported in all animals, with greater incidence and severity observed in mid- and high-dose animals.

Clinical Chemistry: Markedly higher transaminase values (GPT and/or GOT; 324-1460%) were limited to all high-dose rats sacrificed on Day 6 (Table 14). In addition, BUN levels were moderately increased (23-46%) in the same group.

Table 13. Clinical findings in rats dosed for 14 days (6 days for high-dose animals).

	Males			Females		
Dose (mg /kg/d)	15	60	240*	15	60	240*
Hematology						
Leukocyte count						
%Δ vs control group	↓13	↓4	↓68	↓16	↑11	↓53
Lymphocytes w/ cytoplasmic vacuoles						
%Δ vs control group	↓20	↑3900	↑1030	↑40	↑6920	↑2000
Clinical Chemistry						
GPT						
%Δ vs control group	↓5	↓12	↑324	↓2	↓26	↑1260
GOT						
%Δ vs control group	↓20	↓29	↑1460	↑8	↑1	↑1444
BUN						
%Δ vs control group	↑9	↑2	↑ 23	↑2	↓2	↑46

* Data for high-dose group derived from Day 6 due to high mortality. Compared with Day 7 control groups.

Organ Weights: Organ weight assessment was limited to the liver, kidney and lung. Relative liver weights were increased in mid-dose males and high-dose animals (29-30%) and relative kidney weights were increased at the high-dose (34-38%; Table 14). Relative lung weight was also increased in mid- and high-dose females (62 and 31%, respectively).

Gross Pathology: Treatment-related gross tissue/organ changes were observed only in the high-dose groups (Table 14). Changes included discoloration and accentuated lobular markings in the liver, pink/red areas, pale areas in the spleen and white discoloration in the duodenum and/or jejunum. In addition, gaseous distention was noted in various areas of the GI tract (10 of 18) and dry fecal matter was noted in 2 rats. Twelve animals exhibited dried blood or bloody exudate on their faces and four displayed chromodacryorrhea.

Table 14. Gross tissue/organ changes following 14-day SCH 34117 administration in rats.

	Males				Females			
Dose (mg/kg/d)	0	15	60	240*	0	15	60	240*
Relative organ weights (% of body weight)								
Liver								
%Δ vs control group		↓2	↑29	↑29		↑1	↑3	↑30
Kidney								
%Δ vs control group		↑2	↑5	↑34		↑2	↑4	↑38
Lung								
%Δ vs control group		↑5	↑13	↑8		↑4	↑62	↑31
Gross pathology n=	**5**	**5**	**5**	**9**	**5**	**5**	**5**	**9**
Liver - discoloration	0	0	0	7	0	0	0	6
- markings	0	0	0	3	0	0	0	1
Lungs - pink/red	0	0	1	5	1	0	1	5
Spleen - pale	0	0	0	1	0	0	0	1
Duodenum/jejunum								
-white discoloration	0	0	0	3	0	0	0	1
Colon - dry fecal matter	0	0	0	1	0	0	0	1
Face - dry blood/	0	0	0	1	0	0	0	2
- bloody exudate	0	0	0	5	0	0	0	4
Chromodacryorrhea	0	0	0	3	0	0	0	1

* Data for high-dose group derived from Day 6 due to high mortality. Compared with Day 7 control groups.

Histopathology: The histopathology assessment was limited to the kidneys, livers, lungs and pancreas, in addition to organs with gross lesions. Hepatocyte vacuolation was observed in rats from all groups; vacuolation was diffuse in controls but of greater severity and zonal in treated animals (Table 15). Periportal vacuolation was observed in low-and mid-dose animals; vacuolation was centrilobular in high-dose animals. The hepatocytes in the centrilobular region were minimally enlarged in 1/10 low-, 7/10 mid- and 2/18 high-dose animals and mildly enlarged in 4/18 high-dose animals. In addition, the cytoplasm of the hepatocytes in the centrilobular region was basophilic (minimal) in 8/10 low- and 6/10 mid-dose animals. Single cell hepatocyte necrosis was also observed in a mid-dose and high-dose animals.

In the lung, treatment-related histologic observations included the presence of foam cells in pulmonary alveoli in animals from all treatment groups, as well as congestion, edema and mild acute pneumonia in high-dose rats. Vacuolation of the cortical tubular epithelium of the kidney was also noted in mid- and high-dose animals, as well as necrosis of the cortical and medullary tubular epithelium in high-dose animals. In addition, vacuolation of acinar cells in pancreas was present in all high-dose rats, as well as in the jejunum epithelium of one high-dose animal. Hyperactive goblet cells and the presence of cellular debris were present in the jejunum of another high-dose animal and hypoactive germinal centers in the mesenteric lymph node of one high-dose animal and in spleens of two high-dose animals were also reported.

Table 15. Histopathological changes following 14-day SCH 34117 administration in the rat.

	Males				Females			
Dose (mg/kg/d)	0	15	60	240*	0	15	60	240*
Liver								
-hepatocyte vacuolation	5	5	5	9	5	5	5	9
-single cell necrosis	0	0	1	5	0	0	0	3
-congestion	0	0	0	2	0	0	0	4
Lung								
-foam cells (alveoli)	0	0	4	9	0	4	5	9
-congestion	0	0	0	6	0	0	0	5
-edema	0	0	0	1	0	0	0	3
-mild pneumonia	0	0	0	0	0	0	0	1
Kidney								
-CTE vacuolation	0	0	0	8	0	0	3	5
-necrosis	0	0	0	6	0	0	0	4
-congestion	0	0	0	2	0	0	0	2
Pancreas - acinar cell vac.	0	0	0	9	0	0	0	9

* Data for high-dose group derived from Day 6 due to high mortality.
CTE: cortical tubular epithelium

Toxicokinetics: Table 16 summarizes the results of the toxicokinetic analysis. Plasma levels were similar in both males and females and increased sub-proportionally with increasing dose. Plasma levels in mid-dose animals on Day 13 were approximately — those reported on Day 1, indicating that drug accumulation may occur with increasing doses. Less than 7.5% of the drug was recovered as SCH 34117 in the 24-hour urine samples throughout the study.

Table 16. Plasma levels of SCH 34117 in the rat.

Dose (mg/kg/d)	Day	3-hr plasma concentration (ng/ml)		Day	24-hr urinary recovery (%)	
		Males	Females		Males	Females
15	1			1	2.35	4.80
	13			12	2.45	3.43
60	1			1	2.90	3.63
	13			12	2.23	7.1
240	1			1	1.15	1.45
	13	*	*	12	*	*

* High dose rats died or were sacrificed prior to Day 12.

A NOAEL could not be selected for this study due to adverse findings at the lowest dose and an incomplete histologic assessment. The target organs of toxicity identified in this study were the liver, lung, kidneys and pancreas, although other target organs may not have been identified due to the incomplete assessment.

Monkey, 14-day Oral Toxicity

Report No.: P-6527 *Study No.*: 97015 *Volume*: 1.7

Study Dates: Starting date 2/3/97; report issued 12/22/97
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration: 0.32-1.3 mg SCH 34117/ml; 1.6 mg loratadine/ml
Dose Volume: 5 ml/kg/day
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

Methods: Cynomolgus monkeys (juvenile to young adult; males: 3.1-3.9 kg; females: 2.2-3.2 kg) were assigned to the following treatment groups:

Dose (mg SCH 34117 /kg/day):	0	1.6	3.2	6.5	**8 mg loratadine/kg/day**
No./sex	3	3	3	3	3

Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine (equimolar to high dose of SCH 34117) by oral administration for 14 to 16 days. The following observations were made:

Clinical observation . . . daily
Body weight . . . . . weekly
Food consumption . . . . daily
Water consumption . . . not assessed

Ophthalmoscopy	once pretest and Day 10
Veterinary exam.	once pretest and Day 10
Physical examination	once pretest and Day 8; includes body temperature, respiratory rate, heart rate, blood pressure and ECG
Hematology	once pretest and Day 9/10
Clinical chemistry	once pretest and Day 9/10
Urinalysis	once pretest and Day 9/10
Enzyme induction	livers from control, comparative control (loratadine), and SCH 34117 mid- and high-dose groups (n=3/group) assayed for protein content, cytochrome P-450 content, 7-pentoxyresorufin O-dealkylase (PROD) activity, 7-ethoxyresorufin O-deethylase (EROD) activity, 7-ethoxycoumarinO-deethylase and benzphetamine N-demethylase (BND) activity
Organ weights	at sacrifice; (for specific organs see Addendum, page 31)
Gross pathology	at sacrifice
Histopathology	at sacrifice; organs/tissues from vehicle control, comparative control and high-dose SCH 34117, rats dying prior to scheduled necropsy and all gross lesions (for specific tissues/organs see Addendum, page 31).
Toxicokinetics	Day 1 and during Week 2; samples collected at 20 and 40 min and 1, 1.5, 2.5, 4, 8, 12 and 24 hours post-dose on Days 1 and 10; measured using [redacted] · LOQ = [redacted]ng/ml)

Results: Results are summarized in tables 17-20.

Mortality: None.

Clinical Observations: No treatment-related effects were observed. The presence of soft-feces in one mid-dose female once during Week 1 was considered to be an incidental finding.

Body Weight: No toxicologically significant treatment-related effects were observed.

Food Intake: No toxicologically significant treatment-related effects were observed.

Physical examination: No toxicologically significant treatment-related effects on body temperature, respiratory rate, heart rate, blood pressure and ECG.

Ophthalmoscopy: No toxicologically significant treatment-related effects were observed.

Veterinary examination: No toxicologically significant treatment-related effects were observed. Incidental findings included alopecia of legs, desquamation of nasal skin, menses and sores/wounds.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects were observed other than a dose-dependent increase in triglyceride levels (25-126%) in SCH 34117-treated males (Table 17). Levels in high-dose males were increased by 62% prior to dosing, indicating a net

increase of 64% after dosing. In addition, males administered loratadine showed a 44% increase in triglyceride levels compared to controls. However, prior to dosing, levels were increased by 56%, resulting in a net decrease of 12%.

Urinalysis: No toxicologically significant treatment-related effects other than a dose-related increase (60-121%) in the urine osmolarity of SCH 34117-administered males (Table 17).

Table 17. Clinical findings in monkeys administered SCH 34117.

	Males					Females				
Dose (mg /kg/d)	0	1.6	3.2	6.5	Lorat.	0	1.6	3.2	6.5	Lorat.
Clin. Chemistry										
Triglycerides										
%Δ vs control group		↑25	↑56	↑126	↑44		↑28	↑113	↓14	↑34
Urinalysis										
Osmolarity										
%Δ vs control group		↑60	↑85	↑121	↑30		↑2	↓8	↓24	↑8

Organ Weights: No toxicologically significant treatment-related effects.

Enzyme Induction: Administration of high-dose SCH 34117 produced a slight induction of liver microsomal cytochrome P-450 enzymes that was comparable to that of loratadine (Table 18; PROD activity was increased by 73% in males and 80% in females, respectively). However, neither compound altered absolute or relative liver weight, cytochrome P-450 content or benzphetamine N-demethylase or 7-ethoxycoumarin. Microsomal protein content (mg/g) was also unaltered except for a slight, but significant, increase (13%) in high-dose females.

Table 18. Enzyme induction in monkeys administered SCH 34117.

	Males					Females				
Dose (mg/kg/d)	0	1.6	3.2	6.5	Lorat.	0	1.6	3.2	6.5	Lorat.
Microsomal prot. (mg/g liver)	22.6	20.8	22.5	21.2	24.0	21.8	21.4	22.6		24.1
Enzyme Induction										
PROD (pmol/min/mg mic. prot.)	1.1	0.9	1.3			2.5	3.2	3.4		
EROD (pmol/min/mg mic. prot.)	469	569	540			304	433	602		

Shaded areas indicate a significant difference from vehicle controls.

Gross Pathology: No toxicologically significant treatment-related effects were observed.

Histopathology: No definitive toxicologically significant treatment-related effects were observed. However, numerous findings with unclear dose-responses and low severity were noted (Table 19). A true assessment of these findings was not possible since animal numbers were small and the sponsor failed to examine low- and mid-dose tissue in cases in which the high-dose incidence was greater than that of control groups. However, the observed findings are not considered to be of great concern, especially due to the low severity and similarity to findings observed with the active loratadine control group.

Table 19. Histopathological changes after 14-day administration in monkey.

	Males				Females			
Dose (mg/kg/d)	0	3.2	6.5	Lorat.	0	3.2	6.5	Lorat.
Histology* **n=**	**3**	**1**	**3**	**3**	**3**	**1**	**3**	**3**
Eye - mci	0		1(1)	0	0		1(1)	2(1)
Brain - mci	2(1)		3(1)	1(1)	2(1)		2(1)	2(1)
- mineralization	0		2(1)	2(1)	1(1)		0	2(1)
Sciatic nerve - inflamm	0		0	0	0		1(1)	0
Sal gland: mandib								
- mci	1(1)	1(1)	2(1)	2(1)	2(1)		3(1)	3(1)
- sialolith	0		0	0	0		1(1)	0
Mandib Lymph node								
- hemorrhage	0		0	1(1)	0		1(1)	1(1)
- sinusoidal eos.	0		1(2)	0	1(1)		0	1(1)
Trachea - pigment	0		0	0	0		1(1)	0
Thyroid gland								
- follicular cyst	0		1(2)	2(1.5)	0		0	1(1)
Esophagus - mci	0		1(1)	1(1)	0		0	1(1)
Thymus - hemorrhage	0		1(1)	0	0		0	1(1)
Tongue - glossitis	0		2(1.5)	0	0		0	1(1)
Heart - mci	1(1)		3(1.3)	2(1)	3(1)		1(1)	2(1)
- fibrosis	0		1(1)	0	0		0	0
- vacuolation	0		1(1)	0	0		0	0
- eos. Infilt.	1(1)		2(1)	1(2)	0		0	1(1)
Aorta - intimal prolif	0		1(2)	0	0		0	0
Stomach - mci	0		2(1)	1(1)	1(1)		0	0
- inflammation	1(1)		1(2)	1(1)	0		0	0
- gland. ectasia	0		0	0	0		1(1)	0
Duodenum - pigment	0		1(1)	1(1)	0		0	1(2)
Liver - Kup cell pigment	0		0	0	0		1(1)	1(1)
Spleen - lymph hyperpl	1(1)		2(1.5)	1(1)	1(1)		0	2(2)
- pigment	0		0	0	0		1(1)	1(1)
Pancreas - mci	1(1)		0	0	0		2(1)	0
- congestion	0		0	0	0		1(1)	0
Kidneys-nephritis(tubule)	1(2)		2(1)	1(1)	0		1(1)	2(1.5)
- mci	3(1)		3(1)	2(1)	2 (1)		3(1)	3(1)
-mac pigment	0		0	0	0		1(1)	0
-med. Int. basophilia	0		0	0	1(1)		2(1)	1(1)
Adrenal cortex								
- hypertrophy/focal	0		0	0	0		1(1)	0
Urinary bladder(inflamm)	0		1(1)	0	0		0	0
Skeletal muscle-inflamm	0		0	0	1(2)		2(2)	0
Bone marrow - lym fol	0		1(1)	0	0		0	1(1)
Lung - foamy alv mac	0		2(1)	2(1)	1(1)		1(1)	0
- mineralization	0		1(2)	0	0		0	0
- vasculitis	0		1(1)	0	0		0	0
- bronchitis	0		1(1)	0	0		0	0
Prostate - mci	0		2(1)	2(1)	0		0	0
Skin - mci	0		0	0	1(1)		2(1)	0
- inflammation	0		0	0	0		1(1)	0
Mammary gland - cyst	2(1.5)		1(2)	2(1)	1(1)		2(1.5)	1(2)
Ovaries - mineralization					1(1)		2(1.5)	2(1)
Uterus - adenomyosis					0		1(1)	0

* Incidence(severity). Severity based upon 0-4 scale in which 0, 1, 2, 3, 4 indicate none, minimal, mild, moderate or severe, respectively. **mci**: monocellular infiltration.

Toxicokinetics: Table 20 summarizes the results of the toxicokinetic analysis in which plasma levels were measured using [redacted]. Exposures to SCH 34117 increased sub-proportionally with dose in males following oral administration on Day 1 as 2- and 4-fold increases in dose resulted in 1.5-fold and 1.9-fold increases, respectively, in exposure. In females, however, a 2-fold increase in dose resulted in proportional increase in exposure, while a 4-fold dose increase resulted in supra-proportional increase in exposure. However, exposure levels in males at the two lower doses were consistently greater (2- to 5-fold) than those in females. Exposures were not significantly different between Days 1 and 14 at the two lower SCH 34117 doses, although evidence of drug accumulation was present at the high dose. Maximum plasma concentrations also increased sub-proportionally compared to dose. Mean T_{max} was achieved between 2.5-8 hours following SCH 34117 administration and the terminal phase half-life was approximately 7.5-12 hours.

Administration of 8 mg/kg/d loratadine produced greater exposures to SCH 34117 than to the parent compound (6.7- and 7.4-fold in females and males, respectively) on Day 1, increasing to 13- and 36-fold, respectively, by Day 14. Exposures were less than those observed following high-dose SCH 34117 administration (65-80%). Similar to SCH 34117 administration, SCH 34117 exposure was greater in males (~1.6-fold) and greater on Day 14 than on Day 1 (1.3-fold).

Table 20. 14-day toxicokinetics of SCH 34117 and loratadine in the monkey.

Dose (mg/kg/d)	Analyte	Day	$t_{½}$ (hr)	T_{max} (hr)	C_{max} (ng/ml)	AUC(tf)[a] (ng.h/ml) Males	Females	Avg.
1.6 (SCH 34117)	SCH 34117	1	10.2	4	79	1670	614	1142
		14	11.9	2.5	103	2030	395	1213
3.2 (SCH 34117)	SCH 34117	1	ND	4	149	2502	869	1566
		14	8.37	8	97.7	1874	961	1417
6.5 (SCH 34117)	SCH 34117	1	7.83	2.5	227	3187	3250	3172
		14	7.77	8	342	5697	4532	5112
8 (Loratadine)	SCH 34117	1	7.06	2.5	84.1	1108	687	898
		14	ND	4	114	1434	905	1169
	Loratadine	1	3.1	1.5	46.1	150	102	126
		14	1.67	1.5	18.6	39.8	67.3	54

[a] AUC(tf) values calculated using the mean concentration data (generally 2 males and 2 females at each timepoint).

The high-dose of 6.5 mg SCH 34117/kg/day was identified as the NOAEL for this study due to the low incidence of significant findings and the lack of any clear dose-response effects. Target organs of toxicity were not identified at the selected doses in this study.

Summary of Toxicology

Acute, oral and intraperitoneal studies were performed in mice and rats, as well as an oral study in monkeys. 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 (hypoactivity, ataxia, convulsions, tremors, prostration) and respiratory system (gasping, increased respiratory rate) in mice and rats, and the gastrointestinal system (emesis, diarrhea) in monkeys.

Subacute, oral studies were performed for 14 days in rats (low-dose study: 1, 4 and 8 mg/kg SCH 34117 and 10 mg/kg loratadine; high-dose study: 15, 60 and 240 mg/kg SCH 34117) and monkeys (1.6, 3.2 and 6.5 mg/kg SCH 34117 and 8 mg/kg loratadine). In the low-dose rat study, no target organs of toxicity were observed and the NOAEL was identified as 8 mg/kg. In the high-dose study, however, the identified target organs of toxicity were the liver, lung, kidneys and pancreas, although not all target organs may have been identified due to the limited histological examination included in this study. Observed toxicities included increased liver, lung and kidney relative weights associated with histologic findings (vacuolation, necrosis, congestion and foam cells). Other findings included clinical signs at the high dose (chromodacryorrhea, chromorhinorrhea, slow righting reflex, salivation), reduced body weights and food consumption), increased leukocyte counts, and increased levels of GPT, GOT and BUN). Since adverse findings were observed at all doses tested, a NOAEL was not identified for this study. In the monkey, no target organs of toxicity were clearly identified, although a number of histologic findings were of slightly increased incidence at the high-dose compared to controls. Since the sponsor did not evaluate tissues from animals administered lower doses and since small numbers of animals were used, it was not possible to clearly discern the significance of the findings. Other findings in the monkey included increased triglyceride levels and urine osmolarity, as well as increased levels of EROD and PROD. The high dose of 6.5 mg/kg was selected as the NOAEL for this study.

Addendum: Histopathology inventory for IND [redacted]

Study No.	P-6526	D18289	P-6527
Duration	14-day	14-day	14-day
Species	rat	rat	monkey
Adrenals	X*		X*
Aorta	X		X
Bone marrow smear	X		X
Bone (femur)	X		X
Bone (rib)			X
Bone (strenum)	X		X
Brain:	X*		X*
Cecum	X		X
Cervix			
Colon	X		X
Duodenum	X		X
Epididymis	X*		X*
Esophagus	X		X
Eye	X		X
Fallopian tube			
Fat			
Gall bladder			X
Gross lesions	X	X	X
Harderian gland	X		
Heart	X*		X*
Hyphophysis			
Ileum	X		X
Injection site	NA	NA	NA
Jejunum	X		X
Kidneys	X*	X*	X*
Lacrimal gland			X
Larynx			
Liver	X*	X*	X*
Lungs	X*	X*	X*
Lymph nodes, cervical			
Lymph nodes (LALN)			
Lymph nodes, mandibular	X		X
Lymph nodes, mediastinalis			
Lymph nodes, mesenteric	X		X
Mammary gland	X		X
Nasal cavity			
Optic nerves			
Ovaries	X*		X*
Oviduct			
Pancreas	X	X	X
Parathyroid	X		X
Peripheral nerve			
Pharynx			
Pituitary	X*		X*
Prostate	X*		X*
Rectum			
Salivary gland	X*		X*
Sciatic nerve	X		X
Seminal vesicles	X		X
Skeletal muscle	X		X
Skin	X		X
Spinal cord	X		X
Spleen	X*		X*
Stomach	X		X
Testes	X*		X*
Thoracic Limb	X		
Thymus	X*		X*
Thyroid	X*		X*
Tongue	X		X
Trachea	X		X
Urinary bladder	X		X
Uterus	X*		X*
Uterine horn			
Vagina	X		X

* Organ weight obtained

REPRODUCTIVE TOXICOLOGY

Rat (oral) Pilot Segment I Reproductive Toxicity Study

Report No.: P-6821 *Study No.*: 97111 *Volume*: 1.16

Study Dates:	Starting date 9/12/97; report issued 2/10/98
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration:	1.2-9.6 mg SCH 34117/ml
Dose Volume:	5 ml/kg/day
GLP:	The study was an unaudited report.
QA report:	No.

Methods: Crl:CD(SD)BR VAF/Plus rats were assigned to the following treatment groups:

Dose (mg /kg/day):	0	6	24	48
No./sex	8	8	8	8

All rats were dosed once daily by esophageal intubation. Males were dosed for 21 days prior to mating and throughout the mating period. Females were dosed for 14 days prior to and throughout mating until Gestation Day 7. After the premating dosing period, each female was placed with a male from the same dose group for seven days. Each morning, females were checked for evidence of mating, at which time mated females were housed individually. In the absence of mating after seven days, females were placed with a proven male from the same dose group for up to seven additional days.

Results: Results are summarized in Table 21.

Mortality: One high-dose female was found dead on the first day of mating (15 days of dosing). Death was associated with large fecal pellets for five days followed by a period of reduced fecal pellets and a 7.4% body weight loss during the first week of dosing which was not regained.

Clinical signs: Reduced stool and large fecal pellets were noted in mid- and high-dose animals, primarily during the premating dosing period. No stool was observed in one high-dose animal.

Body weight: Premating body weight gain of high-dose males and females was reduced (59 and 116%, respectively). The high-dose treatment effect was still present in females during the gestation period as body weight gain was reduced by 54% compared to control animals on Gestation Day 6. By Gestation Day 14, body weight gain was reduced by 18%. May be related to reduced food consumption since this was observed at a similar dose in an embryo-fetal development study in rats.

Necropsy: No abnormal findings were observed.

Mating and fertility indices: Reduced male and female mating indices (43 and 29%, respectively) were noted at the high-dose. However, there were no clear effects on fertility. Also, an increased time to identify positive evidence of mating (143 to 325%) was noted at the mid- and high-dose.

Vaginal cytology: No abnormalities were observed.

Uterine/ovarian exam: Effects were limited to the high-dose group (data was available for 4 females) and included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal. Reduced implantation sites and fetuses/animal in the mid-dose group were due to decreases in one animal and are not considered drug-related.

Table 21. Results of Pilot Segment I reproductive study in rats.

	Males				*Females*			
Dose (mg/kg)	***0***	***6***	***24***	***48***	***0***	***6***	***24***	***48***
Body wt gain, premating								
% Δ vs control		↓18	↓11	↓59		↑28	↑34	↓116
Body wt gain, gestation Day 6								
% Δ vs control						↓18	↓8	↓54
Clinical observations								
Premating period:								
-reduced stool	0	0	0	5	0	0	2	7
-large fecal pellets	0	0	4	5	0	0	8	5
-chromorhinorrhea	0	1	0	2	0	0	0	0
Gestation period:								
-reduced stool					0	0	0	1
-large fecal pellets					0	0	2	0
Precoital Interval								
% Δ vs control						↑17	↑143	↑325
Mating Index (%)								
% Δ vs control		no Δ	no Δ	↓43		no Δ	no Δ	↓29
Fertility Index (%)								
% Δ vs control		no Δ	↓13	↓13		no Δ	↓13	↓20
Corpora lutea (#/animal)								
% Δ vs control						↓2	↓6	↓21
Implantation sites (#/animal)								
% Δ vs control						↓3	↓26	↓23
Fetuses (#/animal)								
% Δ vs control						↓1	↓28	↓38
Resorption (#/animal)								
% Δ vs control						↓33	↑11	↑233
Preimplantation loss								
% Δ vs control						↑39	↑789	↑39
Postimplantation loss								
% Δ vs control						↓33	↑11	↑233

A NOAEL of 24 mg/kg was identified in this study, while the lethal dose was 48 mg/kg. Thus, the oral high-dose in the definitive rat fertility study should be less than 48 mg/kg, in concurrence with the sponsor's conclusion. It should be noted that ICH Guidelines for Detection of Toxicity to Reproduction (ICH S5A and S5B) recommend premating administration for males

to be at 4-weeks in duration assuming that a toxicity study of at least 1-month duration demonstrates no effects on spermatogenesis (premating administration of 9-10 weeks in the case of positive findings); the present dose-ranging study included a 3-week premating administration for males. The sponsor should consult the ICH Guidelines when performing the definitive Segment I study.

Rat (oral) Pilot Segment II Reproductive Toxicity Study

Report No.: P-6718 *Study No.*: 97113 *Volume*: 1.16

Study Dates:	Starting date not provided; report issued 12/22/97
Testing Lab:	Schering-Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration:	0.6-9.6 mg SCH 34117/ml
Dose Volume:	5 ml/kg/day
GLP:	This report was unaudited.
QA report:	No.

Methods: Crl:CD(SD)BR VAF/Plus female rats (~12 weeks old) were assigned to the following treatment groups:

Dose (mg /kg/day):	0	3	12	24	48
No./dose group	6	6	6	6	6

All rats were dosed once daily by esophageal intubation from Days 6-15 after mating.

Results: Results are summarized in Table 22.

Mortality: None.

Clinical signs: None

Body weight: Maternal body weight gain was dose-dependently reduced during the dosing period (significant in upper-middle and high-dose animals, 52 and 72%, respectively; $p<0.01$).

Necropsy: No abnormal findings were observed.

Uterine/ovarian exam: All rats were pregnant and the numbers of corpora lutea, implantations, resorptions and fetuses in SCH 34117-treated groups were comparable to the control group.

Fetal body weight: The mean fetal body weights in the high-dose group were significantly lower ($p<0.01$) than the controls (12.5%).

Fetal examination: Other than the presence of an omphalocele in one upper-middle dose fetus, no abnormal changes were observed. This malformation is considered to be a common finding in rats and not a drug-related effect.

Table 22. Results of Pilot Segment II reproductive study in rats.

	Females				
Dose (mg/kg)	*0*	*3*	*12*	*24*	*48*
Maternal body wt gain -dosing period					
% Δ vs control		↓5	↓28	[redacted]	
Fetal body wt					
% Δ vs control		↓4	↓4	↓9	[redacted]

Drug treatment did not induce adverse clinical effects and was not teratogenic in the offspring. A NOAEL of 12 mg/kg was identified in this study based upon the significant reduction in maternal body weight gain observed in upper-mid and high-dose animals. The high-dose in the definitive embryo-fetal development rat study should not exceed 48 mg/kg due to the combined reduction in maternal and fetal body weights observed in the high-dose group.

Rabbit (oral) Dose Range-finding Segment II Reproductive Toxicity Study

Report No.: P-6719 *Study No.*: 97115 *Volume*: 1.16

Study Dates: Starting date 7/18/97; report issued 2/4/98
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139; purity = 99.8%) in 0.4% (w/v) aqueous methylcellulose
Concentration: 12.5-150 mg SCH 34117/ml
Dose Volume: 2 ml/kg/day
GLP: This report was unaudited.
QA report: No.

Methods: Hra (NZW) SPF rabbits (females; ~ 6 months of age; unmated in Phase I and mated in Phase II) were assigned to the following treatment groups:

Dose (mg /kg/day):	0	25	50	100	150	225	300
No./dose group - Phase I	1		1	1	1	1	1
No./dose group - Phase II	4	4	4	4			

All rats were dosed once daily by gastric intubation. In Phase I, rabbits were given 2 to 7 doses depending upon when signs of toxicity occurred. In Phase II, mated female rabbits were dosed from Day 7 through Day 19 after mating.

Results:

Phase I: Deaths occurred at doses ≥ 150 mg/kg/day (7 doses at 150 mg/kg, 3 doses at 225 mg/kg and 2 doses at 300 mg/kg). At 150 and 225 mg/kg, reduced stool was observed prior to death. Animals given 100 or 50 mg/kg were dosed for 5 or 3 days, respectively, and observed for