

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-300

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

Labeling Review

NDA NUMBER: 21-300 & 21-563
SERIAL NUMBER: 27-FEB-2004 Supplement
PRODUCT: Clarinex® (desloratadine) Syrup
INTENDED CLINICAL POPULATION: Children (0.6 – 11 yr) with Allergic rhinitis
SPONSOR: Schering-Plough
DOCUMENTS REVIEWED: labeling (proposed)
REVIEW DIVISION: Division of Pulmonary and Allergy Drug Products (HFD-570)
PHARM/TOX REVIEWER: Luqi Pei, Ph.D.
REVIEW COMPLETION DATE: August 16, 2004

REVIEW

The nonclinical sections of the proposed labeling for Clarinex® syrup are acceptable. Schering proposed a revised labeling for their desloratadine products on February 27, 2004. The revisions were in the sections of clinical disciplines. The nonclinical sections have been considered acceptable previously. The current submission contains no nonclinical data. The new, additional clinical data do not warrant any revision of the nonclinical sections of the desloratadine. An approval of the syrup dosage and the proposed labeling of desloratadine is recommended from the nonclinical viewpoint.

There are currently 8 desloratadine NDAs that are for approved and marketed products or that are under the review by the Agency. Table 1 presents an overview of these applications. The products include Clarinex® tablets, Reditabs® tablets and syrup. The tablets (5 mg/tablet) are adult dosage while the syrup is the pediatric dosage. Syrup doses are age-adjusted. The systemic exposures of the pediatric patients are similar to that of the adults, based on plasma drug area-under-curve concentrations.

Table 1. Desloratadine Products on the Market or in Development

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

a. A combination product of desloratadine and pseudoephedrine that is not listed as a desloratadine product in the COMIS database.

This review covers both NDAs 21-300 and 21-563, because they are indicated for almost identical populations. (NDA 21-300 is indicated for children 2 – 11 years of age while NDA 21-563 is for children 6 months to 11 years of age). Previous reviews have determined both applications are approvable from the nonclinical perspective. These documents are reviews by Dr. Timothy McGovern dated September 1, 2000 in NDA 21-300 and by Dr. Huiqing Hao dated May 12, 2003 in NDA 21-563. Neither review identifies any outstanding approvability issues although both reviews identify a 2-yr carcinogenicity study of desloratadine in mice as a phase 4 commitment. The study has been completed and submitted under IND 21-605. Its results should be incorporated into the labeling when the Center's Executive Carcinogenicity Assessment Committee completes its evaluation of the results.

The proposed labeling for the nonclinical sections of the desloratadine syrup application is identical to that for the approved Clarinex tablet label and is acceptable, as concluded in Dr. Hao's review dated May 12, 2003 in NDA 21-563. Dr. McGovern conducted the original labeling review of desloratadine in a review dated September 29, 2000 in NDA 21-165 (an application for a desloratadine tablet dosage). The Agency approved the labeling as recommended by Dr. McGovern on December 21, 2001 in NDA 21-165.¹ Dr. Hao concluded that the syrup and tablet products could carry an identical labeling. Dr. Hao's conclusion was based on the clinical finding that the systemic exposure of pediatric patients to desloratadine from the syrup was similar to that of adult from the tablets. The current submission does not contain any new or additional nonclinical data. The new clinical data confirm the previous finding that the systemic exposures of pediatric patients to desloratadine from the syrup are similar to that of tablets in adults (personal communications during the 06-AUG-04 NDA wrap up meeting). There is no necessity to modify Dr. Hao's conclusion and the proposed labeling is acceptable.

The additional clinical data, however, identify a significant difference in desloratadine metabolism in patient subpopulations. Patients are categorized as normal and poor metabolizers. The poor metabolizers show plasma drug AUCs six times the normal metabolizers. However, the poor metabolizers are only a small fraction of the whole

¹ Dr. McGovern deferred the labeling review for NDA 21-300.

population. Whether and how the labeling can reflect this difference on metabolic rate was discussed in the 06-AUG-04 wrap up meeting. It was determined that the animal to human dose ratios of the labeling will be based on the normal metabolizers. The possibility of stating specifically that the animal to human dose ratios are based on normal metabolizers was also considered. It was felt that this would adversely impact the legibility of an already complex labeling of the nonclinical sections. The benefit of adding this information may not outweigh its adverse impact. In addition, the labeling of other drugs [fluoxetine (Prozac) and loratadine] with similar scenarios did not identify the poor metabolizers in the nonclinical sections. Overall, it is felt that there is no significant need to specifically identify the poor metabolizers in this application.

Based on the above discussions, desloratadine syrup (NDAs 21-300 and NDA 21-563) is recommended for approval from the nonclinical perspective.

The sponsor's proposed labeling for the relevant nonclinical sections is shown below:

CLINICAL PHARMACOLOGY:

...

INDICATIONS AND USAGE:

CLARINEX is indicated for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) in patients of 6 months of age and older.

PRECAUTIONS:

...



2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Luqi Pei
8/16/04 02:01:28 PM
PHARMACOLOGIST

Timothy McGovern
8/16/04 02:29:46 PM
PHARMACOLOGIST
I concur.

RECOMMENDATION

The NDA for descarboethoxyloratadine is approvable from a preclinical standpoint with the incorporation of the aforementioned change to the label.

Timothy J. McGovern, Ph.D., Pharmacologist

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
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/s/

Timothy McGovern
9/26/01 03:04:52 PM
PHARMACOLOGIST

Joseph Sun
10/1/01 08:30:09 AM
PHARMACOLOGIST
I concur.

**HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Label Review #1**

NDA No. 21-165

Submission Date: 04 OCT 2000

Reviewer: Timothy J. McGovern, Ph.D.

Review Completed: 19 OCT 2000

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

Sponsor: Schering Plough Corp.

Drug Names: CLARINEX Code Name: Descarboethoxyloratadine

Background: The sponsor submitted a response to Division revisions of the sponsor's proposed label for Clarinex. In regards to the preclinical sections of the label, the sponsor's comments focused primarily on the ability of Clarinex and metabolites to cross the blood-brain barrier, a new section entitled "**Pharmacodynamics: Effects on QTc:**" which combines preclinical and clinical findings, changes in the method of estimating animal to human exposure multiples for carcinogenicity, reproductive toxicity and overdosage sections, the removal of information regarding rodent liver tumors in the Carcinogenicity section, and revisions of the rat fertility section to include findings previously described in the Pregnancy section. These issues are addressed below. In addition, Dr. Badrul Chowdhury, the MO Supervisor, recommended the deletion of the second paragraph of the Mechanism of Action section under the Clinical Pharmacology section since the statement is difficult to place in a clinical context and since other antihistamines do not include such statements.

LABELING REVIEW:

In the section entitled "Clinical Pharmacology", the sponsor proposes that the phrase "demonstrates limited crossing of desloratadine across the blood-brain barrier." be replaced by "demonstrate that desloratadine does not readily cross the blood-brain barrier since this terminology is used in the loratadine label and since tissue distribution data of drug-derived radioactivity in rat brain following single oral doses of ¹⁴C-loratadine or ¹⁴C-desloratadine were virtually identical. The sponsor's proposal is acceptable. Thus, the following changes should be made:

MECHANISM OF ACTION:

Desloratadine is a long acting tricyclic antihistamine antagonist with selective H₁-receptor histamine antagonist activity. Receptor binding data indicates that at a concentration of 2 – 3 ng/ml (7 nanomolar), desloratadine shows significant interaction with the human histamine H₁ receptor.



6 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

OVERDOSAGE:

RECOMMENDATIONS

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.

Timothy J. McGovern, Ph.D., Pharmacologist

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

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
18	21998	99990.91	141	93	60% of 30 mg/kg dose in 1 month tox study
rabbit: embryo-fetal					
60 mg/kg	12987	NA	228	NA	Embryo-fetal rabbit study
Overdosage					
rat-250 mg/kg	27441	124731.82	175	116	1-week Pk study at 240 mg/kg; M+F
Carcinogenicity					
Mouse - 40 mg/kg	1861	5029.73	7	3	28-day dietary study w/lorradine
Mouse - 192 mg/kg	33516	90583.78	127	49	3-mos screening study
Rat - 25 mg/kg	7017	31895.45	45	30	28-day dietary study w/lorradine
Rat - 10 mg/kg	1619	7359.09	10	7	28-day dietary study w/lorradine
QTc:					
Monkey - 24 mg/kg	54346	NA	955		3-mos monkey (P6976) at 24 mg/kg
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			

Drug: **Clarinet**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric				0	3	0.00	25	0.00
Adult	>12		5 1	5	50	0.10	37	3.70

	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
<u>Carcinogenicity:</u>								
rat			6	0	---	---	---	---
mouse			3	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
<u>Reproduction and Fertility:</u>								
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
dog			20	0	---	N/A	---	N/A
dog			20	0	---	N/A	---	N/A
<u>Teratogenicity:</u>								
mouse			3	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
<u>Overdosage:</u>								
mouse	oral	353	3	1059	286.2	---	290	---
rat			6	0	---	---	---	---
dog			20	0	---	---	---	---
rabbit			12	0	---	---	---	---
<u>Other: (Overdosage)</u>								
rat			6	0	---	---	---	---
guinea pig			8	0	---	---	---	---
monkey	oral	250	12	3000	810.8	---	810	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

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

KEY WORDS: Anti-histamine

NDA No. 21-165

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

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

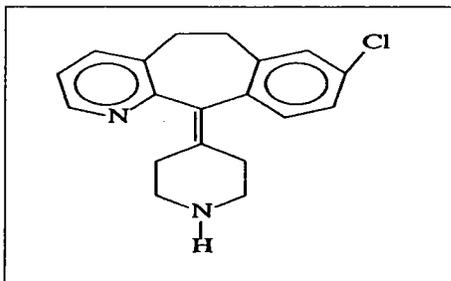
Information to be Conveyed to Sponsor: Yes (✓), No ()

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

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

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

Structure:



Empirical Formula: C₁₉H₁₉ClN₂

Molecular Weight: 310.82

Drug Class: Anti-histamine

Indication: Seasonal allergic rhinitis

Proposed Clinical Dose: 5 mg once daily in adults and children 12 years of age and older. In a 50 kg adult this is 0.25 mg/kg or 6.2 mg/m².

Drug Product Formulation: 5 mg tablet

Ingredient	Core tablet (mg)
Desloratadine	
Corn starch, NF	
Dibasic calcium phosphate dihydrate USP	
Microcrystalline cellulose NF	
Talc USP	
Opadry II Blue 32B10817	
Opadry II Clear YS-1-19025A	
Carnauba wax NF	
White wax NF	
Water purified USP	
Pelletized dry ice	

Total tablet weight

106.61

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

Route of Administration: Oral (tablet)

Related INDs/NDAs:

IND 55,364 – descarboethoxyloratadine tablets

IND 21,249

IND 41,897

NDA 19-658

NDA 20-704

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

IND 55,364: Descarboethoxyloratadine tablets

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

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

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

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

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

NDA 19658: Loratadine tablets

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

Preclinical Studies Submitted and Reviewed in this NDA:

Study	Res. Report #/ Reference #	Vol.
<i>New Pharmacology – Schering Study Reports:</i>		
Inhibition of ³ H-pyrimilamine binding to the histamine H ₁ -receptor by loratadine	SN 30372	1.7
Inhibition of ³ H-pyrimilamine binding to the histamine H ₁ -receptor by desloratadine (SCH 34117) and other loratadine metabolites	SN 30279	1.7
Topical antihistamine activity of loratadine, SCH 34117 and levocabastine	D-27083	1.7
MDS Panlabs biochemical assays report	D-28718	1.7
Effect of SCH 34117 on tumor necrosis factor α production.	D-28727	1.7
Inhibition of cytokine generation and mediator release by human basophils treated with desloratadine	SN 30853	1.7
Descarboethoxyloratadine (DCL) and eosinophil chemotaxis and adhesion to endothelial cells, and production of superoxide anions and leukotriene C4 from human blood eosinophils.	SN 30854	1.8
Antissussive activity of desloratadine (SCH 34117, DCL) and loratadine in the guinea pig	D-30053	1.8
Effects of desloratadine (SCH 34117, DCL) and loratadine on nasal congestion in the cat		
The effect of oral SCH 34117 on the response to <i>Ascaris</i> challenge in allergic cynomolgus monkeys.	D-30026	1.8
<i>New Pharmacology – Publications and References:</i>		
Kleine-Tebbe J, Josties C, Frank G et al. Inhibition of IgE and non-IgE-mediated histamine release from human basophil leukocytes in vitro by a histamine H ₁ -antagonist, desethoxycarbonyl-loratadine. <i>J Allergy Clin Immunol.</i> 1994; 93: 494-500.	1	1.7
Berthon B, Taudou G, Cobettes L et al. In vitro inhibition by loratadine and descarboethoxyloratadine of histamine release from human basophils and of histamine release and intracellular calcium fluxes in rat basophilic leukemia cells. <i>Biochem Pharmacol.</i> 1994; 47: 789-794.	2	1.7
Genovese A, Patella V et al. Loratadine and desethoxycarbonylloratadine inhibit the immunological release of mediators from human FcεRI+ cells. <i>Clin Exp Allergy.</i> 1997; 27: 559-567.		
Lippert M, Kruger-Krasagakes S et al. Pharmacological modulation of IL-6 and IL-8 secretion by the H ₁ -antagonist descarboethoxyloratadine and dexamethasone by human mast and basophil cell lines. <i>Exp Dermatol.</i> 1995; 4: 272-276	3	1.7
Lebel B, Bousquet J et al. Loratadine reduces RANTES release by an epithelial cell line. <i>J Allergy Clin Immunol.</i> 1997; 99: S44 (abstract).	4	1.7
Paubert-Braquet M and Czarlewski W. Effect of loratadine and SCH 34117 on superoxide anion production from human polymorphonuclear neutrophils and monocytes. <i>J Allergy Clin Immunol.</i> 1994; 93: 257 (abstract).	5	1.7
Molet S, Gosset P et al. Inhibitory activity of loratadine and descarboethoxyloratadine on histamine-induced activation of endothelial cells. <i>Clin Exp Allergy.</i> 1997; 27: 1167-1174.	6	1.7
<i>New Safety Pharmacology Studies and Publications:</i>		
Ancillary pharmacology of SCH 34117		
Effects of loratadine metabolites on cardiovascular function in rats		
Electrocardiographic effects of intravenous SCH 34117 in the guinea pig		
The comparative effects of quinidine and non-sedating antihistamines on HERG (I Kr) channels expressed in <i>Xenopus</i> oocytes.	SN 30063 P-5429	1.8 1.8
One-week oral (gavage) cardiovascular study of SCH 34117 in cynomolgus monkeys	D-28578 D-28717	1.8 1.8
A.E. Lacerda, M-L. Roy, E.W. Lewis and D. Rampe. Interactions of the non-sedating antihistamine loratadine with a Kv1.5 type potassium channel cloned from human heart. <i>Mol. Pharmacol.</i> 52, 314-322, 1997	SN 98558	1.10
Effects of Sch 34117 on respiratory function in conscious rats.	8	1.8
<i>New Pharmacokinetic (ADME) Studies:</i>		

Study	Res. Report #/ Reference #	Vol.
SCH 34117: Pharmacokinetics, metabolism and excretion of ¹⁴ C-SCH 34117 following a single oral dose to male and female mice.	SN 30650	1.8
SCH 29851: Pharmacokinetics, metabolism and excretion of ¹⁴ C-SCH 29851 following a single oral dose to male and female mice.	SN 97308	1.36
SCH 29851: A 3-week toxicokinetic study with SCH 29851 administered as a drug-diet mixture to male and female mice.	SN 97311	1.37
SCH 34117: Pharmacokinetics, metabolism and excretion of ¹⁴ C-SCH 34117 following a single oral or intravenous dose to male and female albino rat.	SN 99076	1.39
SCH 29851: Pharmacokinetics, metabolism and excretion of ¹⁴ C-SCH 29851 following a single oral dose to the male and female albino rat.	SN 97307	1.40
One week oral (gavage) toxicokinetic study of SCH 34117 and loratadine (SCH 29851) in rats.	SN 97310	1.42
SCH 29851: A three week toxicokinetic study of SCH 29851 administered as a drug-diet mixture to male and female rats.	P-6938	1.45
A three week toxicokinetic study with SCH 29851 or SCH 34117 administered orally to male and female rats.	SN 99077	1.46
SCH 34117: A two week toxicokinetic study with SCH 29851 or SCH 34117 administered orally to female New Zealand white rabbits.	SN 99078	1.47
SCH 34117: Pharmacokinetics, metabolism and excretion of ¹⁴ C-SCH 34117 following a single oral or intravenous dose to the male and female cynomolgus monkeys.	SN 99080	1.49
SCH 29851: Pharmacokinetics, metabolism and excretion of ¹⁴ C-SCH 29851 following a single oral dose to the male and female cynomolgus monkeys.	SN 97309/ SN98452	1.51
SCH 34117: Toxicokinetic study of single oral (gavage) dose of SCH 34117 or SCH 29851 in cynomolgus monkeys.	SN 97312/ SN 98452	1.53
SCH 34117: A three week toxicokinetic study of SCH 29851 or SCH 34117 administered orally to male and female cynomolgus monkeys.	P-6815	1.55
SCH 34117: In vitro binding of SCH 34117 to mouse, rat, monkey and human plasma proteins using ultrafiltration.	SN 99079	1.56
In vitro metabolism of SCH 29851 and SCH 34117 by rat, mouse, monkey, rabbit and human using hepatocytes, tissue slices and/or microsomes.	SN 99215	1.58
Interim report: In vitro metabolism of SCH 29851 and SCH 34117 in rat and mouse liver microsomes and S(fractions from normal and Aroclor-treated animals.	SN 97304	1.58
<i>New Genetic Toxicology Studies:</i>		
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<i>New Reproductive Toxicology:</i>		
Oral (gavage) fertility study of SCH 34117 in rats	SN 99287	10.8
Fertility study of SCH 34117 administered by oral gavage in male rats	SN 99241	10.8
Oral (gavage) embryo-fetal developmental toxicity and toxicokinetic study in rats		
Oral perinatal and postnatal development study of SCH 34117 in rats	P-6891	1.28
Oral embryo-fetal development study of SCH 34117 in rabbits	SN 98552	1.29
	P-6922	1.31
	SN 97117	1.33
	P-6802	1.32

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

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

Study	Res. Report #	Vol.	Date of Review
Two-week oral (gavage) range-finding toxicity and toxicokinetic study of SCH 34117 and SCH 29851 in rats.	P-6526	1.11	5/22/1998
Two-week oral (gavage) range-finding toxicity study of SCH 34117 and SCH 29851 with toxicokinetics in cynomolgus monkeys.	P-6527	1.14	5/22/1998
Four-week oral (gavage) toxicity study of SCH 34117 in rats.	P-6965	1.17	10/27/1998
Four-week oral (gavage) toxicity study of SCH 34117 in cynomolgus monkeys.	P-6974	1.19	10/27/1998
Three-month oral (gavage) toxicity study of SCH 34117 in rats.	P-6973	1.23	1/31/2000
Three-month oral (gavage) toxicity study of SCH 34117 in cynomolgus monkeys.	P-6976	1.26	1/31/2000
Genetic Toxicology Studies:			
Bacterial mutagenicity study of SCH 34117.	P-6609	1.34	5/22/1998
Chromosome aberration study of SCH 34117 in human peripheral blood lymphocytes.	P-6692	1.35	5/22/1998
Mouse bone marrow erythrocyte micronucleus study of SCH 34117.	P-6912	1.35	1/31/2000
Reproductive Toxicology:			
Pilot oral (gavage) fertility study of SCH 34117 in rats.	P-6821	1.28	5/22/1998
Pilot oral embryo-fetal development study of SCH 34117 in rats.	P-6718	1.31	5/22/1998
Dose-range finding study of SCH 34117 in female rabbits.	P-6719	1.32	5/22/1998
Pilot (oral) perinatal and postnatal development study of SCH 34117 in rats	P-6817	1.33	12/15/1998

Studies Submitted but Not Reviewed in this NDA Submission:

Study	Res. Report #	Vol.
SCH 29851/SCH 34117: Validation of a gas liquid chromatographic method for the quantitative determination of SCH 29851 and SCH 34117 in mouse plasma.	P-6977	1.62
Determination of loratadine and SCH 34117 in mouse plasma by gas chromatography.	P-6482	1.63
SCH 29851/SCH 34117/SCH 45581: Validation of an HPLC-mass spectrometric method for the determination of SCH 29851, SCH 34117 and SCH 45581 in mouse plasma.	SN99094	1.63
Determination of loratadine and SCH 34117 in rat plasma by gas chromatography.	P-6481	1.64
SCH 29851 and SCH 34117: Validation of a gas liquid chromatographic method for the determination of SCH 29851 and SCH 34117 in rat plasma.	P-6898	1.65
SCH 29851/SCH 34117/SCH 45581: Validation of an HPLC-mass spectrometric method for the determination of SCH 29851, SCH 34117 and SCH 45581 in rat plasma.	SN 99095	1.66
SCH 29851 and SCH 34117: Validation of a gas liquid chromatographic method for the determination of SCH 29851 and SCH 34117 in rabbit plasma.	P-6708	1.66
SCH 29851/SCH 34117/SCH 45581: Validation of an HPLC-mass spectrometric method for the determination of SCH 29851, SCH 34117 and SCH 45581 in rabbit plasma.	SN 99096	1.67
SCH 29851 and SCH 34117: Validation of a gas liquid chromatographic method for the determination of SCH 29851 and SCH 34117 in cynomolgus monkey plasma.	P-6997	1.67
SCH 29851: Validation of a gas liquid chromatographic method for the determination of SCH 29851 (loratadine) and SCH 34117 in cynomolgus monkey plasma.	P-6131	1.68
SCH 29851/SCH 34117/SCH 45581: Validation of an HPLC-mass spectrometric method for the determination of SCH 29851, SCH 34117 and SCH 45581 in monkey plasma.	SN 99097	1.68
SCH 45581: Validation of an HPLC-mass spectrometric method for the determination of total SCH 45581 in monkey plasma.	SN99108	1.69
SCH 29851/SCH 34117: Validation of a gas liquid chromatographic method for the quantitative determination of SCH 29851 and SCH 34117 in rat plasma.	P-6947	1.69
Seven-day oral (gavage) toxicity study of SCH 34117 in cynomolgus monkeys	SN 98488	1.9
Four-week oral (gavage) toxicity study of SCH 34117 in cynomolgus monkeys*	P-6975	1.21

*: Study P-6975 was not reviewed since the two highest doses (36 and 72 mg/kg) were administered for only 2-3 consecutive days due to a high incidence of emesis. The low dose (12 mg/kg) was evaluated over a 28 day period in Study P-6974 which assessed doses of 3, 6, and 12 mg/kg SCH 34117 and 12 mg/kg SCH 29851.

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

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

PHARMACOLOGY:

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

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

Table 1. Receptor binding assays:

Cell/Model type	Report #/ Reference	Activity																	
Rat brain membrane	SN 30372	SCH 34117 was ~ 20-fold more potent than loratadine, but comparable to chlorpheniramine, in inhibiting binding of [³ H]pyrilamine to rat brain H1 receptor. Ki = 4.8, 86 and 3.7 nM, respectively.																	
	SN 30279	SCH 34117 and its hydroxylated metabolites showed similar potency in inhibiting binding of [³ H]pyrilamine to rat brain H1 receptor while the conjugated glucuronide of the 3-OH-DCL metabolite displayed reduced potency by over 100-fold. <table border="1"> <thead> <tr> <th>Compound</th> <th></th> <th>Ki (nM)</th> </tr> </thead> <tbody> <tr> <td>SCH 34117</td> <td>DCL</td> <td>7.0</td> </tr> <tr> <td>SCH 39090</td> <td>6-OH DCL</td> <td>4.5</td> </tr> <tr> <td>SCH 39091</td> <td>5-OH DCL</td> <td>9.5</td> </tr> <tr> <td>SCH 45581</td> <td>3-OH DCL</td> <td>13</td> </tr> <tr> <td>SCH 354202</td> <td>3-OH DCL gluc</td> <td>19% at 2 μM</td> </tr> </tbody> </table>	Compound		Ki (nM)	SCH 34117	DCL	7.0	SCH 39090	6-OH DCL	4.5	SCH 39091	5-OH DCL	9.5	SCH 45581	3-OH DCL	13	SCH 354202	3-OH DCL gluc
Compound		Ki (nM)																	
SCH 34117	DCL	7.0																	
SCH 39090	6-OH DCL	4.5																	
SCH 39091	5-OH DCL	9.5																	
SCH 45581	3-OH DCL	13																	
SCH 354202	3-OH DCL gluc	19% at 2 μM																	
Various species target receptors	D-28718	<u>Receptor type</u>	<u>IC50 (nM)</u>	<u>Ki (nM)</u>															
		Histamine H1, central	17	5.7															
		Histamine H1, peripheral	168	13															
		Histamine, H2	360	353															
		Muscarinic M1	208	50															
		Muscarinic M2	131	47															
		Muscarinic M4	493	104															
		Muscarinic M5	445	320															
Serotonin 5-HT7	369	204																	

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

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

Cell/Model type	Report #/ Reference	Activity
Inhibition of superoxide production in human neutrophils and monocytes	Ref. 6	SCH 34117, but not loratadine, inhibited superoxide anion production by PMN induced by fMLP or PAF at > 1 μ M with almost complete inhibition at 50 μ M. Both drugs inhibited superoxide anion production by monocytes induced by PMA or zymosan at > 0.1 and 1 μ M, respectively. Effective concentrations are greater than those required to block H1 receptors suggesting response is unrelated to receptor interaction.
Inhibition of endothelial cell activation, P-selectin expression and IL-6 and IL-8 in human umbilical vein endothelial cells	Ref. 7	SCH 34117 and loratadine inhibited histamine-induced (10^{-4} M) activation of endothelial cells: Similar inhibition of P-selectin expression (IC_{50} = 13x 10^{-9} M and 23x 10^{-9} M, respectively). IL-6 and IL-8 inhibition: SCH 34117 displayed greater potency (IC_{50} = 2.6x 10^{-12} M and 10^{-9} M, respectively) than loratadine (IC_{50} = 0.3x 10^{-6} M and 0.2x 10^{-6} M, respectively)
Inhibition of chemotaxis, and leukotriene and superoxide production in human eosinophils and secretion of interleukins and TNF- α by monocytes	SN 30854	Eosinophils: Attenuated chemotaxis in response to PAF with maximum attenuation of 36% at 10 μ M and adhesion (25% at 10 μ M). No effect noted on leukotriene production at a concentration of 10 μ M. 10 μ M inhibited PMA-stimulated and spontaneous superoxide generation Monocytes: SCH 34117 (100 nM to 10 μ M) did not inhibit secretion of IL-4, -5, -13, -10, -1B, -16 and TNF- α by PBMC.
Inhibition of histamine release in leukocytes from allergic and nonallergic subjects	1	IgE-mediated and calcium ionophore A23187-induced histamine release inhibited by SCH 34117 in dose-dependent fashion (IC_{30} = 6-11 μ mol/L). Higher SCH 34117 concentrations induced mediator release. Rapid onset of inhibition at 10 μ mol/L.
Inhibition of histamine release in human basophils and rat basophilic leukemia cells	2	Dose-dependent inhibition of histamine release observed at doses above 2 μ M SCH 34117 and 7 μ M loratadine in anti-IgE triggered human basophils and DNP-triggered rat basophilic leukemia cells. Inhibition by loratadine increased when extracellular Ca $^{2+}$ reduced from 1.8 to 0.45 μ M. Both drugs (2.5-25 μ M) inhibited the cytosolic Ca $^{2+}$ rise induced by DNP-BSA challenge in rat cells which may inhibit mediator release.
Inhibition of histamine, LTC $_4$, PGD $_2$ and tryptase release in human Fc ϵ RI+ cells from peripheral blood, skin or lung tissue	3	SCH 34117 and loratadine (3x 10^{-6} to 10^{-4} M) inhibited release of histamine and LTC $_4$ (5-40%) following pre-incubation before Der p 1 antigen or anti-Fc ϵ RI challenge. 10-40% inhibition of histamine and LTC $_4$ and PGD $_2$ release from lung tissue cells activated by anti-Fc ϵ RI. 10-40% inhibition of histamine, tryptase, LTC $_4$ and PGD $_2$ release from skin cells challenged with anti-Fc ϵ RI.
Inhibition of IL-6 and IL-8 release in human mast cell line (HMC-1) and basophilic cell line (KU812)	4	SCH 34117 (10^{-14} to 10^{-5} M) dose-dependently suppressed IL-6 release by up to 40% and IL-8 release by up to 50% after 1 hr preincubation followed by PMA and Ca-ionophore A23187 stimulation. Dexamethasone (10^{-11} to 10^{-6} M) inhibited release by 60-80%.
Inhibition of TNF- α production in human peripheral blood cells	D-28727	Weak inhibitory activity against TNF- α production (7-24% at 0.1 to 10 μ M) following LPS-stimulation. Rolipram significantly more potent (IC_{50} = 0.035-0.12 μ M).
Inhibition of RANTES release in nasal polyp	5	SCH 34117 and loratadine (10 μ M, added 15 minutes prior to activation) significantly reduced RANTES release (~ 70% and 40%, respectively)

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

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

Table 3. *In vivo* functional assays.

Model	Reference	Activity												
Inhibition of nasal response to histamine challenge in anesthetized guinea pig	D-27083	Levocabastine >>>SCH 34117 >>loratadine in inhibiting nasal response (increase in microvascular permeability) to histamine challenge; SCH 34117 10-fold more potent than loratadine. <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Compound</th> <th>ED50 (μg)</th> <th>Max. efficacy/concentration</th> </tr> </thead> <tbody> <tr> <td>Levocabastine</td> <td>0.025</td> <td>85%/1 μg</td> </tr> <tr> <td>SCH 34117</td> <td>0.9</td> <td>69%/3 μg</td> </tr> <tr> <td>Loratadine</td> <td>8.7</td> <td>49%/10 μg</td> </tr> </tbody> </table>	Compound	ED50 (μ g)	Max. efficacy/concentration	Levocabastine	0.025	85%/1 μ g	SCH 34117	0.9	69%/3 μ g	Loratadine	8.7	49%/10 μ g
Compound	ED50 (μ g)	Max. efficacy/concentration												
Levocabastine	0.025	85%/1 μ g												
SCH 34117	0.9	69%/3 μ g												
Loratadine	8.7	49%/10 μ g												
Inhibition of capsaicin-induced cough in guinea pigs	SN 30053	SCH 34117 and loratadine (10 mg/kg, po, each) did not attenuate the number of coughs induced by aerosolized capsaicin. Both inhibited cough in ovalbumin sensitized guinea pigs with a minimum effective dose of 0.3 and 1 mg/kg, po, respectively.												
Effect on compound 48/80-induced congestion	SN 30026	Neither SCH 34117 nor loratadine (3 mg/kg, iv) displayed decongestant effects on congestion induced by aerosolized compound 48/80.												
Effect on allergen- and histamine-induced bronchospasm in monkeys	D-28686	SCH 34117 (5 mg/kg, po) reduced allergen-induced bronchospasm, heightened resistance (~60%) and reduced compliance (~20%) and histamine induced bronchospasm (normal and allergic monkeys). No effect was noted after 24 hours on allergen-induced increase in BAL cells.												

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

SAFETY PHARMACOLOGY:

The results of new safety pharmacology studies submitted to this NDA are summarized in Table 4. SCH 34117 induced no significant in vivo cardiovascular effects in rats or monkeys (doses up to 12 mg/kg, oral, or 10 mg/kg, intraperitoneal) or in guinea pigs (25 mg/kg, IV). In vitro assessments showed that SCH 34117 was ~ 7-fold less potent than loratadine in blocking Kv1.5 channel in HEK 293 cells and loratadine (10 μ M) failed to significantly alter HERG currents. Loratadine and SCH 34117 (up to 10 μ M) had minimal effects on I_{HERG} current (15-20%) compared to terfenadine and quinidine (IC_{50} = 82 and 168 nM, respectively). SCH 34117 had no effect on the gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg in rats.

Table 4. Summary of safety pharmacology studies.

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

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

PHARMACOKINETICS AND TOXICOKINETICS:

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

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

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

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

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

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

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

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

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

Parameters	Oral administration						
	Radioactivity			SCH 34117			
	Males	Females	Combined	Males	Females	Combined	
C _{max} (ng equiv/ml)	1957	1476	1668	206	266	242	
T _{max} (hr)	4	2.67	3.2	4	2	2.8	
AUC (tf) (ng equiv.hr/ml)	24534	14184	18324	2639	2390	2490	
T _{1/2} (hr)				11.3	8.25	9.46	
F (%)				57.1	47.1	51.1	
F _a (%)	105	78.5	89.2				
Cl/F (L/hr.kg)				2.7	12	8.29	
Parameters	IV administration						
	C _{max} (ng equiv/ml)	1409	1653	1531	704	1073	888
	T _{max} (hr)	2	1.33	1.67	0.083	0.083	0.083
	AUC (tf) (ng equiv.hr/ml)	19758	18532	19145	3642	4294	3968
	T _{1/2} (hr)				11.2	11.6	11.4
	V _{area} (L/kg)				35.4	39.3	37.3
	CL (L.hr/kg)				2.43	2.58	2.5

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

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

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

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

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

Parameters	Males	Females	Combined
Drug-derived radioactivity in plasma			
Cmax (ng equiv/ml)	519	542	505
Tmax (hr)	4	1	1
AUC (tf) (ng equiv.hr/ml)	7290	6941	7115
SCH 34117 in plasma			
Cmax (ng/ml)	319	310	278
Tmax (hr)	1	2	1
AUC(tf) (ng.hr/ml)	2502	2412	2449
T1/2 (hr)	4.67	3.71	4.17
Cl/F (L/hr.kg)	2.69	2.88	2.78

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

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

Parameters	Males	Females	Combined
Drug-derived radioactivity in plasma			
Cmax (ng equiv/ml)	2134	1879	1817
Tmax (hr)	0.5	1	0.5
AUC (tf) (ng equiv.hr/ml)	15120	19910	17560
SCH 29851 in plasma			
Cmax (ng/ml)	67	53.1	52.8
Tmax (hr)	0.5	0.25	0.25
AUC(tf) (ng.hr/ml)	87.6	70.1	78.1
T1/2 (hr)	1.37	1.04	1.18
Cl/F (L/hr.kg)	97	121	109
SCH 34117 in plasma			
Cmax (ng/ml)	117	65.8	89.3
Tmax (hr)	3	1	3
AUC(tf) (ng.hr/ml)	805	584	705
T1/2 (hr)	6.2	4.05	6.14

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 16. Comparative protein binding of SCH 34117.

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

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

In rats, a single dose of SCH 34117 (6.5 mg/kg) was extensively metabolized via mono- or dihydroxylation at primarily the 5- and/or 6- positions although high levels of unchanged SCH 34117 were observed (Table 17). Male rats achieved high circulating levels of SCH 357130, a heretofore unknown C11-pyridine N-oxide derivative. Minor metabolites included SCH 45581, SCH 45581-glucuronide and other unknown compounds. Profiles from urine, bile and feces were similar. No SCH 34117 specific metabolites were noted compared to loratadine (Table 18).

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

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

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5- OH-SCH 34117

e: 5,6-dihydroxy-SCH 34117

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

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

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

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

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

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5-OH-SCH 34117

e: 5,6-dihydroxy-SCH 34117

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

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

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

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

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

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5-OH-SCH 34117

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

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

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

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5-OH-SCH 34117

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

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

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

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5- OH-SCH 34117

e: covalent adduct (N-formyl derivative)

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

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

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

a: blood collection time

b: not detected

c: 6-OH-SCH 34117

d: 5- OH-SCH 34117

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

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

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

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

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

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

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

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

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

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

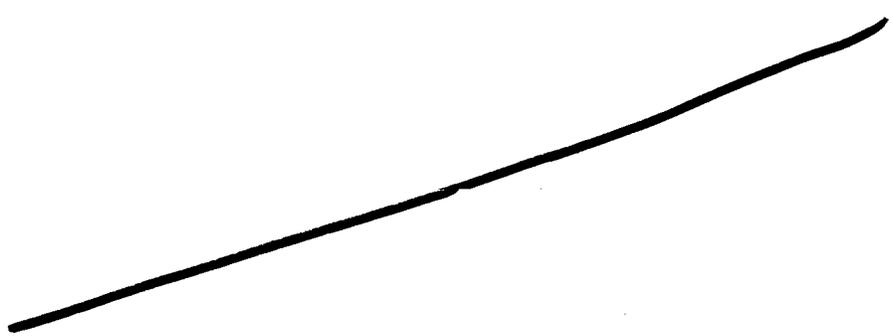
to trace levels of SCH 45581 (3-OH-SCH 34117) and SCH 45581-glucuronide and several unknowns were also detected. Male rats achieved relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. In vitro studies confirmed the results of the in vivo studies and demonstrated that the hydroxylated metabolites are formed in humans although unchanged SCH 34117 was the primary compound detected. Compared to the metabolism profile of loratadine, no SCH 34117-specific metabolites were observed. Excretion of SCH 34117 was primarily via the feces (41-68%) in mice, rats and monkeys with biliary excretion playing a significant role.

TOXICOLOGY:

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

GENETIC TOXICOLOGY:

Genetic toxicology studies assessing SCH 34117 were submitted to IND 55,364 and included a bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay using human lymphocytes and an *in vivo* mouse bone marrow erythrocyte micronucleus assay. SCH 34117 was negative under the conditions tested in each of the assays. The sponsor also submitted two assays (a bacterial reverse mutation assay and an *in vitro* chromosome aberration assay using human lymphocytes) to the NDA as part of their effort to qualify the presence of two synthesis impurities. These studies, which are reviewed below, also produced negative results.





4 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

REPRODUCTIVE TOXICOLOGY:

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

Oral (gavage) fertility study of SCH 34117 in rats

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

Study Dates: Starting date 10/28/1997; report issued 5/8/1999
Testing Lab: Safety Evaluation Center; Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch# 97-34117-X-02RA; purity = 100%) in 0.4% aqueous methylcellulose
Concentration: 1.2-4.8 mg SCH 34117/ml
Dose Volume: 5 ml/kg/day
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

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

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

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

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

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

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

Statistics Deemed unnecessary.

Results:

Mortality: No deaths were reported.

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

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

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

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

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

Estrus cycle: No drug-related effects were observed.

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

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

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

Table 26: Summary of effects on reproductive parameters.

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

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

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

Study No.: 98552 *Volume:* 1.29

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

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

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

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

Male rats were orally administered vehicle or SCH 34117 for 70 days prior to mating and throughout the mating period until euthanasia (total dosing period 106-108 days). Doses were selected based upon results of a pilot study (P-6821, see Original IND 55,364 review) and the fertility study reviewed above. Female rats (25/dose group) were not dosed during this study. The report stated that recovery data would be submitted as an addendum to final report. This data was submitted to IND 55,364 Serial # 159 (dated June 23, 2000) and is reviewed currently. During the mating period, each female was placed in cohabitation with a male for a maximum of 14 days. The following observations were made:

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

Results:

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

Clinical Observations: No drug-related effects were noted.

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

Table 27: Summary of effects on body weight gain.

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

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

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

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

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

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

Table 29: Summary of histopathologic findings in male rats.

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

Minimal	0	0	0	7	3
Mild	0	0	0	0	4
Pituitary gland Vacuolation – cytoplasmic, Rathke's Pouch, macrophage Minimal	2			11	3

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

Table 30: Summary of spermatogenic endpoints.

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

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

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

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

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

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

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

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

Shaded area indicates statistically significant difference from control value.

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

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

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

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

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

Methods: — CD(SD) BR VAF/Plus female rats (11 weeks old; 227-307 g) were assigned to the following treatment groups:

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

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

Dams:

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

Fetuses (F₁):

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

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

Results:**Dams:**

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

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

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

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

Necropsy: No drug-related effects were noted.

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

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

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

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

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

Fetuses (F1):

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

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

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

Shaded area indicates statistically significant difference from control value.

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

Oral embryo-fetal development study of SCH 34117 in rabbits

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

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

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

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

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

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

Dams:

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

Fetuses (F₁):

External exam abnormal conditions, body weights assessed at necropsy
Morphologic exam . . . fetuses internally sexed, assessed for gross visceral changes, and skeletal examinations.
Dead fetuses and resorptions . . examined grossly for external defects and for visceral and skeletal defects.
Statistical analysis Continuous data analyzed by ANOVA; categorical data analyzed Chi-square test

Results:

Dams:

General signs: Drug-related clinical observations included soft stool, reduced numbers of fecal pellets, large fecal pellets or no stool in all SCH 34117-treated groups with increasing incidence occurring at increasing doses.

Body weight: High-dose animals lost weight (0.0007 kg) during dosing period (days 7-19) while control animals gained 0.1731 kg. This finding was most apparent during days 10-16 when high-dose animals lost 0.0393 kg.

Food consumption: Food consumption was reduced in high-dose animals from gestation day 7 onward.

Necropsy: No drug-related findings were observed.

Reproduction Parameters: High-dose animals demonstrated an increased incidence of resorptions compared to control animals (Table 35). In addition, the mean number of fetuses in the high-dose group (7.5) was slightly lower than controls (8.75), although this effect was not statistically significant. These findings may be related to the maternal toxicity observed at the high dose.

Table 35: Effects of SCH 34117 on reproductive parameters following oral administration.

Parameter	Dose (mg/kg)			
	0	15	30	60
Resorptions				
Mean	0.25	0.19	0.33	1
% resorptions	2.8	2.2	3.9	11.8
% animals with resorptions	18.8	11.8	27.8	37.5

Shaded area indicates statistically significant difference from control value.

Toxicokinetics: Systemic exposure to SCH 34117 under the dosing conditions of this study are summarized in Table 36. Exposure increased supra-proportionally with increasing dose and Tmax was achieved within 3-12 hours.

Table 36: Systemic exposure to SCH 34117 following oral administration.

Parameter	Dose (mg/kg)		
	15	30	60
Cmax (ng/ml)	230	456	1166
Tmax (hr)	1	1	3
AUC(0-24 hr) (ng.hr/ml)	1660	4087	12987

Fetuses:

Fetal Gross/Skeletal observations: There were no drug-related fetal gross or visceral malformations or variations except for a slight but statistically insignificant increase in bipartite

sternebra in the high dose group (fetal incidence of 4 and litter incidence of 2 vs 1 and 1, respectively, in controls).

Key study observations: SCH 34117 did not induce any teratogenic effects at the doses up to 60 mg/kg. A NOAEL of 30 mg/kg was identified for maternal and *in utero* effects due to reduced maternal body weight gain and increased incidence of resorption at the high dose. The increased resorption may be a secondary effect due to the severe maternal toxicity observed at the high dose.

Oral peri- and post-natal development study of SCH 34117 in rats

Study No.: 97117 Volume: 1.33

Study Dates: Starting date 1/9/1998; report issued 5/23/1999
Testing Lab: Safety Evaluation Center, Schering Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch# 97-34117-X-02 RA; purity = \bullet) in 0.4% aqueous methylcellulose
Concentration: 0.6-3.6 mg SCH 34117/ml
Dose Volume: 5 ml/kg/day
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

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

Methods: Mated female \bullet CD(SD) BR VAF/Plus rats (12 weeks old; 231-322 g) were assigned to the following treatment groups:

Dose (mg/kg/day)	0	3	9	18
No. of copulated females	25	25	25	25

Female rats (F₀) were placed with males (1:1) for mating until positive evidence of mating was found. The day of mating was designated as Day 0. Mated females received a daily dose of vehicle or test drug by esophageal intubation once a day during the peri-natal (day 6 of gestation) and lactation periods (day 21 postpartum). On day 4 postpartum, the number of offspring per litter was adjusted by randomly selecting 4 male and 4 female offspring, keeping 8 offspring alive when 4 of each sex were not available. No adjustment was made when the number of offspring per litter was less than 8. On day 21 postpartum, one male and female were randomly selected from each litter for postweaning behavioral and developmental measurements, and for later breeding to produce a F₂ generation. The following observations were made:

Dams:

Clinical observation . . . daily from gestation day 0 until lactation day 21
Body weight Days 0, 6, 9, 12, 15, 18 and 21 of gestation and on lactation days 1, 4, 7, 14, and 21.
Food consumption Gestation days 0-6, 6-12, 12-15, and 15-21, and lactation days 1-4, 4-7, 7-10 and 10-14.

- F₀ parturition Assessment for abnormal labor, nursing, or nesting behavior, length of gestation.
- Necropsy Lactation day 21, examined for external and visceral changes and implantation sites.

Offspring (F₁):

- Litter size number of live and dead offspring recorded daily until lactation Day 21. Survival rate calculated for lactation Days 0, 1-4 and 5-21.
- Sex determination pups sexed externally on lactation days 0, 4, and 21
- Clinical observation daily from lactation days 0-21
- Body weight Days 0, 4, 7, 14, and 21 postpartum; weaned F₁ rats weighed weekly until mating, after mating F₁ females weighed on pregnancy Days 0, 6, 9, 12, 15, 18 and 21, and on lactation days 1 and 4.
- Maturation and Behavioral Evaluations
- Surface righting test: lactation day 5 through 12
 - Auditory startle test: lactation day 10 through 15
 - Eye opening: lactation day 12 through 16
 - Incisor eruption: lactation day 9 through 14
 - Negative geotaxis test: lactation day 6 through 10
 - Open field test: lactation days 15, 16 and 17
- Gross visceral exam animals not selected for post-weaning measurements and breeding sacrificed on day 21 of lactation and subjected to gross visceral examination
- F₁ post-weaning measurements one male and female from each litter: body weights measured weekly, observed daily from post-partum day 22 through sacrifice, F₁ females checked for vaginal opening from Day 29 through Day 35 postpartum, F₁ males checked for preputial separation from postpartum day 39 through day 50.
- F₁ estrus cycle determination evaluated from 1 week prior to mating and during mating period by vaginal cytology
- F₁ mating at 11-12 weeks of age, one male from each litter was placed with a female from a different litter within the same dose group for up to 2 weeks. Female was separated once mating occurred. Unmated females paired for up to one more week with a proven male from same dose group.

Offspring (F₂):

- Clinical observation litter size (number born alive and dead), sex, weight and observations, survival calculated until day 4, sacrifice on Day 4, gross external examination.

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

Results:

Dams:

Mortality: There were no SCH 34117-related deaths. Two non-pregnant high-dose females were sacrificed on gestation day 24 when they failed to produce litters.

Clinical Observations: Drug-related clinical findings included soft stool (mid- and high-dose), reduced fecal pellets (high-dose) and large fecal pellets (all doses). In addition, one high dose female had total litter loss and had been eating poorly while another did not appear to be caring for or nursing the pups which were not lively (4 died by day 4).

Body Weight: High-dose dams had a mean weight loss of 4 g during gestation days 6-9 (Table 36). Weight gain was dose-dependently reduced at the two lower doses but findings were not significant. Body weight gain over the entire course of the dosing period, however, was comparable among groups.

Food Intake: Food consumption was reduced by 10-14% in high-dose dams on gestation days 6-12 and lactation days 1-4 (Table 37). Consumption was comparable among all groups at other time points.

Table 37: Summary of effects on clinical findings.

Parameter	Dose (mg/kg)			
	0	3	9	18
Body weight gain (g) - gestation	14	10	5	-4
Food consumption – gestation days 6-12 % change from control values		6	-6	-14
Food consumption (g/animal/d) – lactation days 1-4 % change from control values		-8	-6	-10

Shaded area indicates statistically significant difference from control value.

Parturition: No abnormalities in the length of gestation, number of implantation sites or number of pups per litter were noted in the control group or drug-treated groups.

Necropsy: No remarkable observations were noted following gross and visceral observations.

Offspring (F₁):

Pup survival: The survival rate was at least 99% in all groups on the day of birth but was reduced at the high-dose (92.9%) on days 1-4 (Table 38). Of the 22 that died in the high-dose group, 12 were from one litter and eighteen of the total twenty-eight pup deaths were due to cannibalization. Survival rates were comparable thereafter and no effects on survival were noted during the post-weaning period.

Table 38: Effect of SCH 34117 on pup survival.

Parameter	Dose (mg/kg)			
	0	3	9	18
Survival (%) – days 1 to 4	99.7	98.2	97.7	92.9

Sex determination: Male/female ratios in the treated groups were not affected by treatment of maternal animals.

Clinical observations: No SCH 34117-related findings were observed during the pre-weaning, pre-mating, gestation, and lactation periods.

Body weight: Body weight gain from birth to day 7 or day 21 postpartum was slightly reduced (8-12%) in mid- and high-dose offspring (Table 39). During the pre-mating and F1 gestation periods, no significant effects on body weight gain were noted although body weights of high-dose animals tended to remain below those of control animals.

Table 39: Summary of effects on F₁ clinical findings.

Parameter	Dose (mg/kg)			
	0	3	9	18
Body weight gain: % change from control				
days 0-7 postpartum		-7	-11	-12
days 0-21 postpartum		-5	-8	-9

Shaded area indicates statistically significant difference from control value.

Neurobehavioral/Developmental tests: A dose-related effect on righting reflex was observed as the percentage of pups in each group that was able to right themselves in two seconds was reduced on day 5 at the mid-dose (18%) and up to day 9 at the high-dose (30.3% on day 5, 3.4% by day 9). This effect may be due to the delayed growth of the pups. No effects were noted in tests of auditory startle, eye opening, incisor eruption, vaginal opening, preputial separation, passive avoidance or open field tests.

Estrus cycles: Sponsor states that there were no drug-related findings noted although no data was provided.

Parturition and fertility: All rats in all groups mated. Although the conception rate was reduced at the mid- and high-doses (84 and 86%, respectively vs 100% in control animals), these values fell within the historical range of the laboratory from 1989-1998 (80 to 100%).

Necropsy: No SCH 34117-related gross external and visceral findings were observed in culled and dead F₁ pups or F₁ adults.

Offspring (F2):

No significant differences were noted in body weight on days 0 or 4. Pup survival was reduced at the high-dose (92.9% vs 97.5% in controls) although the finding was not significant. There were no SCH 34117-related gross external or visceral observations.

Key study observations: The NOAEL for developmental toxicity of the F₁ pups was 3 mg/kg due to reduced body weight gain and fetal development effects. A NOAEL of > 18 mg/kg was selected for reproductive indices of the first generation offspring and development of the second generation offspring. A NOAEL of 9 mg/kg was observed for the F₀ dams due to reduced body weight gain and food consumption at the high dose.

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 vertebra, sternbra 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 F₂ generation fetuses. Thus, a NOAEL of 3 mg/kg was selected for developmental toxicity in F₁ pups; a NOAEL of > 18 mg/kg was selected for F₁ reproductive

indices and F₂ 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 H₁ 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 55,364 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 H₁-receptors over H₂ or H₃-receptors and displayed a 14-fold greater affinity for the H₁-receptor than loratadine in cloned H₁ human receptor subtypes (IC₅₀ = 51 and 721 nM, respectively). This finding was confirmed in isolated guinea pig lung tissue (IC₅₀ = 840 and 3030 nM for SCH 34117 and loratadine, respectively). SCH 34117 was also ~ 18-fold more potent than loratadine in rat brain H₁-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 ED₅₀ = 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 M₁ and M₃ receptor subtypes (IC₅₀ = 48 and 125 nM). In a separate study, SCH 34117 showed greatest activity at central H₁ receptors (IC₅₀ = 17 nM) while activity at peripheral H₁ receptors was similar to that at M₂ muscarinic receptors (IC₅₀ = 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, LTC₄ and PGD₂, 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 (ED₅₀ = 0.9 μ g) 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 anti-inflammatory effects of SCH 34117 should be removed since a definitive connection between these properties and the indication of seasonal allergic rhinitis 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 sponsor¹, 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 V_{max} 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 (iK_r) current to ~ ½ control value at 6 x 10⁻⁶ M as the concentration at which ½ current is blocked (k_{0.5}) was 5 x 10⁻⁶ M (k_{0.5} for loratadine was 8.7 x 10⁻⁶). SCH 34117 had no effect at 10⁻⁵ M on inward rectifier current (iK₁) although the curve was flatter at 3 x 10⁻⁵ M; loratadine had more pronounced effect than SCH 34117. Since SCH 34117 has been shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K⁺ channels as well as a cloned human hKv1.5, all findings were observed during in vitro assessments while in vivo studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters, and loratadine-induced cardiac effects have not been observed in humans, SCH 34117 is considered to be reasonably safe in this regard. In terms of general safety pharmacology studies, SCH 34117 induced no effect on the rat gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg.

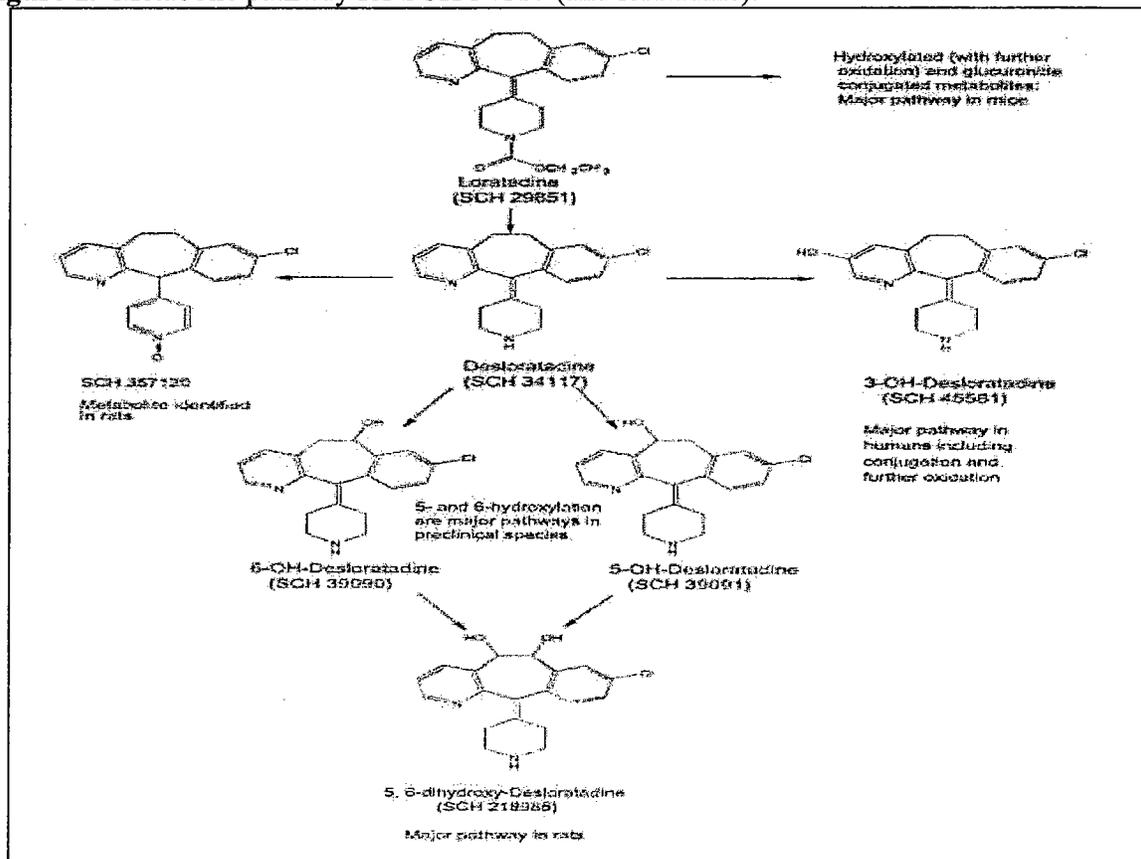
¹ Hey, JA, Del Prado, M, Cuss, FM, Egan, RW, Sherwood, J, Lin, CC, and Kreutner, W. (1995). Antihistamine activity, central nervous system and cardiovascular profiles of histamine H₁ antagonists: comparative studies with loratadine, terfenadine and sedating antihistamines in guinea-pigs. *Clinical and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

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

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

In rats, treatment-related mortality occurred at a dose of 240 mg/kg SCH 34117 in one of two 2-week studies and at a dose of 120 mg/kg in males and 30 mg/kg or greater in females in a three month study. Systemic phospholipidosis was the primary toxicity finding in tissues throughout the body. In addition, kidney necrosis and luminal cellular debris of the epididymides were

observed following 3-month administration. The toxicity profile of SCH 34117 was similar to that of the active control (loratadine) group. However, loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. The NOAEL in the 3-month toxicity study was 3 mg/kg in females and 30 mg/kg in males. These doses resulted in mean systemic exposures ($AUC_{0-24 \text{ hr}}$) of 1890 ng.hr/ml and 9490 ng.hr/ml in females and males, respectively.

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

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

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

next lowest dose tested, 6 mg/kg (~ 140 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose).

An oral peri- and post-natal study was performed in rats. A dose of 3 mg/kg SCH 34117 (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no toxicologically significant effects on F₁ pup survival, pre-weaning growth or F₁ 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 F₂ 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 55,364 and included a bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay using human lymphocytes and an *in vivo* mouse bone marrow erythrocyte micronucleus assay. SCH 34117 was negative under the conditions tested in each of the assays. The sponsor also submitted two assays (a bacterial reverse mutation assay and an *in vitro* chromosome aberration assay using human lymphocytes) to the NDA as part of their effort to qualify the presence of two synthesis impurities. These studies 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 55,354 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 _____, the sponsor performed two genotoxicity assays with SCH 34117 with added levels of _____ 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 _____ impurities to not _____ in the drug substance, or provide further qualification for the drug substance impurities (3 month toxicity study using appropriate levels of impurities _____). The Sponsor submitted information for qualification and their proposed levels (NMT _____ and _____) 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.



5 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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 55,364 Original Review
IND 55,364, Review #2
IND 55,364, Review #3
IND 55,364, Review #4
Minutes of Senior Pharmacology/Toxicology Policy Team
IND 55,364, Review #5
IND 55,364, 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/ortadine
Rat - 25 mg/kg	7017	31895.45	45	30	28-day dietary study w/ortadine
Rat - 10 mg/kg	1619	7359.09	10	7	28-day dietary study w/ortadine
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			

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-300

Review number: 1

Serial number/date/type of submission: NA/December 8, 2000/Original NDA

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

Sponsor and/or agent: Schering Plough Corp., Kenilworth, NJ, USA

Manufacturer for drug substance: Schering Plough Corp., Kenilworth, NJ, USA

Reviewer name: Timothy J. McGovern, Ph.D.

Division name: Pulmonary and Allergy Drug Products

HFD#: 570

Review Completed: 26 SEP 2001

Drug:

Trade Name: CLARINEX Syrup

Generic: Descarboethoxyloratadine (DCL); 0.5 mg/ml

Code Name: SCH 34117

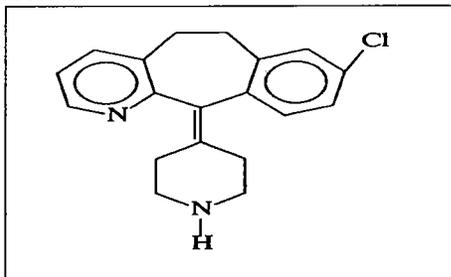
Chemical name: 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)

CAS registry number: NA

Mole file number: NA

Molecular formula/molecular weight: C₁₉H₁₉ClN₂/310.8

Structure:



Relevant INDs/NDAs/DMFs:

IND 55,364 Descarboethoxyloratadine tablets

IND 57,960 Descarboethoxyloratadine syrup

NDA 21-165 Clarinex (Seasonal allergic rhinitis)

NDA 21-297 Clarinex (chronic idiopathic urticaria)

NDA 21-312 Clarinex Reditabs (Seasonal allergic rhinitis and chronic idiopathic urticaria)

NDA 21-313 Clarinex-D (Seasonal allergic rhinitis and congestion)

NDA 21-363 Clarinex (Allergic rhinitis)

Drug Class: Anti-histamine

Indication: Seasonal allergic rhinitis and treatment of chronic idiopathic urticaria

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Clinical Formulation:

Ingredient	(mg/ml)
Desloratadine (SCH 34117), micronized	
Propylene glycol, USP	
Sorbitol solution, USP	
Citric acid anhydrous, USP	
Sodium citrate dihydrate, USP	
Sodium benzoate NF	
Edetate disodium USP	
Sugar granulated	
Natural and art. flavor for bubble gum (#15864)	
Dye FD&C yellow No. 6	
Water purified USP q.s. ad	

Route of Administration: Oral (syrup)

Proposed use: Adults and 12 years of age and over: 2 teaspoonfuls (5 mg) of syrup once daily. Children 6- to 11-years of age: 1 teaspoonful daily (2.5 mg) once daily. Children 2- to 5-years of age: ½ teaspoonful daily (1.25 mg) once daily. In a 50 kg adult this is equivalent to 0.1 mg/kg or 3.7 mg/m²; in a 20 kg child (age 6) this is equivalent to 0.13 mg/kg or 3.13 mg/m²; in a 12 kg child (age 2) this is equivalent to 0.1 mg/kg or 2.6 mg/m².

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

Studies reviewed within this submission: No preclinical studies were submitted to this NDA.

Introduction and drug history: Descarboethoxyloretadine (SCH 34117) is an active metabolite of loratadine, a drug product approved as Claritin in 1993 for the treatment of allergic rhinitis. An NDA for SCH 34117 was submitted for the treatment of seasonal allergic rhinitis in October of 1999 (NDA 21-165) and the NDA was deemed approvable from a preclinical perspective (see attachment). All preclinical pharmacology and toxicology studies conducted with SCH 34117 were reviewed under NDA 21-165. The primary SCH 34117- and loratadine-induced toxicity included systemic phospholipidosis in organ systems throughout the body. The kidney and epididymis were additional targets identified in rats. The Division agreed that the sponsor would not be required to perform chronic toxicity studies with SCH 34117 based upon results of 3-month studies with SCH 34117 in rats and monkeys. However, although CDER's Senior Pharmacology/ Toxicology Policy Group concluded that SCH 34117 was adequately assessed for carcinogenicity in rats in a study performed with loratadine, while a 2 year mouse carcinogenicity study with SCH 34117 should be performed as a Phase 4 commitment.

The excipients sorbitol solution, sodium citrate dihydrate, bubble gum flavor, and dye FD&C yellow No. 6 are components of the Clarinex Syrup formulation that are not included in the Claritin Syrup formulation. However, the sponsor provided adequate safety information for the flavor agent and the other three excipients are proposed at levels below those found in other syrup formulations used for chronic administration.

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

OVERALL SUMMARY AND EVALUATION:

Introduction: Descarboethoxyloratadine (SCH 34117) is an active metabolite of loratadine, a drug product approved as Claritin in 1993 for the treatment of allergic rhinitis. An NDA for SCH 34117 was submitted for the treatment of seasonal allergic rhinitis in October of 1999 (NDA 21-165) and the NDA was deemed approvable pending resolution of CMC concerns (see attachment). All preclinical pharmacology and toxicology studies conducted with SCH 34117 were reviewed under NDA 21-165; primary toxicities include systemic phospholipidosis in organ systems throughout the body. The kidney and epididymis were additional targets identified in rats. Chronic toxicity studies with SCH 34117 were not required based upon results of 3-month studies with SCH 34117. However, CDER's Senior Pharmacology/ Toxicology Policy Group concluded that a 2 year mouse carcinogenicity study with SCH 34117 should be performed as a Phase 4 commitment. Four new excipients are included in this formulation that were not found in the Claritin Syrup formulation; all are included at acceptable levels. The sponsor will be requested to submit updated labeling to conform, where applicable, to the final labeling for NDA 21-165 with the addition of text relating to the indication of chronic idiopathic urticaria. Thus, a review of the product label will be performed at a later time.

Safety evaluation: Adequate safety margins exist for clinical use of SCH 34117 in a syrup formulation for the treatment of seasonal allergic rhinitis and treatment of chronic idiopathic urticaria. The NDA is approvable from a preclinical perspective.

Safety issues relevant to clinical use: None

Other clinically relevant issues: None

Conclusions: This NDA is approvable from a preclinical perspective.

Communication Review:

Labeling review: The review team decided to postpone review of the product label pending submission of updated labeling by the sponsor.

RECOMMENDATIONS:

Internal comments:

1. The NDA for Clarinex syrup for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria is approvable from a preclinical standpoint.
2. The sponsor should submit the final study report for the Phase 4 mouse carcinogenicity study within three years of the NDA 21-165 approval or study initiation, whichever occurs first. This comment was communicated to the sponsor following the review of NDA 21-165.

External comments (to sponsor): None

Reviewer signature:

Timothy J. McGovern, Ph.D.

Team leader signature:

C. Joseph Sun, Ph.D.

Attachments: NDA 21-165 Original Review
NDA 21-165 Label Review #1
Addendum to NDA 21-165 Label Review #1

**HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**

Review #6

IND No. 55,364 **Serial No.** 159 **Submission Date:** 23 JUN 2000

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 28 JUL 2000

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

Sponsor: Schering Corporation, Kenilworth, NJ

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

Class: Anti-histamine

Indication: Seasonal allergic rhinitis

Route of Administration: Oral (tablet)

Related INDs/NDAs: NDA 21-165

Previous Clinical Experience: Phase I, II and III studies in both healthy volunteers and patients with seasonal allergic rhinitis.

Previous Review(s), Date(s) and Reviewer(s):

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998
Review #4	April 1 – October 5, 1999	McGovern	January 31, 2000
Review #5	April 26-November 1, 1999	McGovern	June 7, 2000

The following table summarizes the studies submitted and reviewed in this document:

Preclinical Studies Submitted and Reviewed in this IND:

<u>Study</u>	<u>Report #</u>	<u>Volume</u>
<i>Sub-chronic Toxicology:</i>		
Three-month dose-range finding study of SCH 34117 in mice	SN 97253	44.6
<i>Genetic Toxicology:</i>		
Bacterial mutagenicity study of SCH 45581	SN 99298	44.11
Mouse bone marrow erythrocyte micronucleus study of SCH 45581	SN 99539	44.11

Studies Submitted to the IND but not Reviewed: An addendum to the fertility study in male rats (SN 98552, submitted to NDA 21-165) was submitted to IND 55,364. The review of the addendum which contains recovery data is incorporated with the main study review and can be

found in the Original Review for NDA 21-165. In addition, Study # SN99275: Timing of Onset and Characterization of Testicular Lesions in Mature Rats Administered SCH 32146 (Astemizole) or SCH 32908 (Cetirizine Hydrochloride) for Two Weeks” was not reviewed.

Studies Previously Reviewed: None

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

Sub-Chronic Toxicity:

Mouse, 3-Month Oral (Diet) Dose-Ranging Toxicity Study

Sponsor Study No.: 97523 *Vol.:* 44.6

Study Dates: Starting date: 5/17/1999; summary report issued: 5/22/2000
Testing Lab: Schering Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch IRQ-98-13M1; purity not reported)
GLP: This report included a signed GLP report.
QA report: Yes.

This study was performed to determine doses for an 2 year carcinogenicity study of SCH 34117 in mice.

Methods: Mice (CD-1 ICR BR VAF/Plus; 6 weeks old, 18.9-31 g) were assigned to the following treatment groups:

Dose (mg SCH 34117/kg/day):	Veh. Control	24	48	96	192
No./sex	10	10	10	10	10

SCH 34117 was given orally to mice as a dietary admixture *ad libitum* for 90 to 92 days. The following observations were made:

- Clinical observation . . . assessed daily
- Body weight weekly
- Food consumption weekly
- Test article intake weekly
- Water consumption . . . not assessed
- Health exam not assessed
- Ophthalmoscopy pre-test and Weeks 4 and 12
- ECG not assessed
- Hematology Week 14
- Clinical chemistry Week 14
- Urinalysis not assessed
- Enzyme induction Liver samples assayed for protein content, cytochrome P450 content, 7-pentoxyresorufin O-dealkylase (PROD) activity and 7-ethoxy-resorufin O-dealkylase (EROD)

Organ weights at sacrifice (organs included brain, epididymides, heart, kidneys, liver, lungs, ovaries, salivary glands, spleen, testes, thymus, uterus)
 Sperm analysis assessed in control and mid-high dose males
 Gross pathology at sacrifice
 Histopathology at sacrifice, all tissues were examined in the control (vehicle) and high-dose mice (for specific tissues/organs see Addendum, page 18). Target organs were evaluated to the no-effect level and all tissues from mice that died.
 Toxicokinetics not assessed; sponsor submitted data to NDA 21-165 (6/19/2000) from a 1 month TK study at doses used in current study.

Results:

Mortality: One high-dose male died on day 61 while another high-dose male and one mid-dose female were sacrificed in moribund condition on day 55 and 62, respectively (Table 1). However, the cause of death in the female was not explained and is not clearly related to the administered drug.

Table 1: Total incidence of mortality.

Dose	0	24	48	96	192
<i>(mg SCH 34117/kg/day):</i>					
Males	0	0	0	0	2
Females	0	0	0	1	0

Clinical Observations: Clinical observations were noted in the three highest dose groups and included abnormal stool (large fecal pellets), dehydration, hypoactivity and hunched appearance (Table 2).

Table 2. Clinical observations in mice following 3-month administration.

Observation	Females					Males				
	0	24	48	96	192	0	24	48	96	192
Feces - enlarged	0	0	10	10	10	0	0	10	10	10
Hunched posture	0	0	0	0	3	0	0	0	0	1
Dehydration	0	0	0	0	2	0	0	0	0	1
Hypoactivity	0	0	0	1	1	0	0	0	0	1

Body Weight: Mean body weight gain were reduced by greater than 10% in the three highest dose-groups in males and in high-dose females (Table 3). Surviving high-dose males exhibited mean body weight loss of 1.2 g following the 13-week dosing period.

Table 3: Change in body weight gain following 3-months treatment.

Dose (mg SCH 34117/kg/day):	0	24	48	96	192
Males					
Body weight – start dosing	28.8	28.5	28.3	28.9	28.5
Body weight – end dosing	35.8	36.2	34.4	34	27.3
% Δ in BW gain from control		↑10	↓13	↓27	↓1.2 g
Females					
Body weight – start dosing	21.9	21.6	21.9	21.9	21.5
Body weight – end dosing	28	28.5	29.4	29.6	23.8
% Δ in BW gain from control		↑13	↑23	↑26	↓63

Food consumption: Food consumption (g/animal/day) was reduced up to 22% and 27% in high dose males and females, respectively, compared to control animals throughout the study period.

Test article intake: Mean test article intake values were within 1.1% of the intended intake.

Ophthalmoscopy: No treatment-related findings were reported.

Hematology: Animal numbers in many groups were low (3). Lymphocyte and WBC numbers were reduced in SCH 34117-treated males and a slight decrease in lymphocytes was noted in high-dose females (Table 4).

Table 4. Hematologic findings in mice following 3-month administration.

Hematology	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
	24	48	96	192	24	48	96	192
Lymphocytes % Δ from control	↓21	↓73	↓50	↓76	↑6	↑5	↑9	↓28
WBCs % Δ from control	↓12	↓65	↓40	↓55	↓19	↓20	↑8	↓5

Clinical Chemistry: The liver enzymes ALT, AST and AP were increased dose-dependently up to 6-fold of control values (Table 5). In addition, triglyceride levels were moderately decreased in males and females while glucose and cholesterol levels were decreased in high-dose males. Cholesterol levels were also reduced in upper-mid and high-dose females while BUN was increased in both high-dose males and females.

Table 5. Clinical chemistry findings in mice following 3-month administration.

Parameter	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
	24	48	96	192	24	48	96	192
Glucose								
% Δ from control	↓10	↓2	↓25	↓33	↓12	↑3	↑16	↑10
BUN								
% Δ from control	↓2	↑11	↑1	↑40	↓1	↑13	↑30	↑51
ALT								
% Δ from control	↓10	↑15	↑141	↑636	↓2	↑10	↑99	↑338
AST								
% Δ from control	↓10	↑6	↑58	↑353	↑2	↑15	↑58	↑162
AP								
% Δ from control	↑71	↑50	↑278	↑279	↑9	↑40	↑29	↑75
Cholesterol								
% Δ from control	↓13	↓6	↓1	↓55	↓17	↓3	↓40	↓53
Triglycerides								
% Δ from control	↓24	↓38	↓57	↓77	↓12	↓1	↓39	↓48

Enzyme Induction: Absolute liver weight, liver to body weight ratio and microsomal content were increased at the upper-mid and high doses (Table 6). Relative liver weight was increased at the three highest doses in males. EROD was increased at all doses (significant at the high-dose, 10 to 18-fold) and PROD levels were significantly increased (2.7 to 4.4-fold) at all doses but the highest in males. A similar pattern was noted in females although the levels of increase were not as great (EROD: 1.6 to 7-fold; PROD: 1.7 to 3.8-fold).

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Table 6. Enzyme induction in mice following 3-month drug administration.

	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	24	48	96	192	0	24	48	96	192
Liver weight										
% Δ from control		↑6	↑7	↑17	↑30		↑6	↑9	↑35	↑36
Liver/Body wt ratio										
% Δ from control		↑4	↑12	↑26	↑69		↑6	↑8	↑33	↑64
Microsomal protein (mg/tot liver)										
% Δ from control		↑4	↑11	↑61	↑69		↑19	↑34	↑60	↑111
Cytochrome P450										
% Δ from control										
Nmol/mg microsomal protein		no Δ	no Δ	no Δ	↓30		↑26	↑32	↑37	↓21
Nmol/g liver		↓5	↑3	↑35	↓12		↑45	↑68	↑68	↑95
Nmol/total liver		↑4	↑10	↑59	↑19		↑53	↑84	↑128	↑163
Enzyme Induction										
% Δ from control										
PROD										
pmol/min/mg micros. protein		↑214	↑263	↑175	↓11		↑106	↑280	↑76	↓33
pmol/min/g liver		↑198	↑268	↑266	↑13		↑134	↑240	↑111	↑7
pmol/min/total liver		↑222	↑298	↑337	↑49		↑148	↑272	↑184	↑43
EROD										
pmol/min/mg micros. protein		↑180	↑150	↑312	↑992		↑58	↑90	↑160	↑233
pmol/min/g liver		↑160	↑151	↑439	↑1298		↑81	↑134	↑212	↑526
pmol/min/total liver		↑181	↑173	↑542	↑1715		↑90	↑154	↑526	↑603

Shaded areas indicate statistically significant difference from control group ($p < 0.05$).

Western blot analysis demonstrated a dose-related induction of CYP2B1/2 and CYP1A2 and that Cytochrome P-450 4A was increased at the two highest doses in males. Only protein levels of CYP2B1/2 were increased at all doses in females. The reduced activity of PROD at the higher doses suggests that CYP2B1/2 may be inhibited at very high doses of SCH 34117.

Sperm Analysis: Mean sperm counts and concentrations of testicular spermatids or epididymides caudal sperm were not influenced by administration of the mid-high dose of SCH 34117.

Organ Weight: A dose-related increase in absolute and relative liver weight was observed at the upper-mid and high-doses (Table 7). Relative lung weight was also increased at the high dose. In addition, absolute and relative thymus weights were decreased at the high dose while uterine weight was decreased at the upper-mid and high-doses.

Table 7. Organ weight changes in mice following 3-month administration.

Organ weight	Males				Females			
	24	48	96	192	24	48	96	192
Liver								
AOW-% Δ from control	5	6	15	29	7	13	36	40
RTB-% Δ from control	5	12	26	71	6	11	34	69
Lungs								
AOW-% Δ from control	5	-5	5	10	no Δ	6	11	11
RTB-% Δ from control	5	no Δ	14	46	1	1	8	36
Thymus								
AOW-% Δ from control	-7	-7	-17	-41	-29	3	-19	-47
RTB-% Δ from control	-7	-2	-10	-22	-30	1	-21	-36
Uterus								
AOW-% Δ from control					-14	-18	-33	-48
RTB-% Δ from control					-14	-20	-38	-39

AOW: Absolute organ weight

RTB: Relative to body weight

Gross Pathology: Gross findings included distention in the gastrointestinal tract, discoloration of the kidney, and reduced size of the uterus primarily at the highest dose (Table 8). Kidney discoloration was the only finding with a histological correlate (necrosis) other than systemic phospholipidosis.

Table 8. Gross observations in mice following 3-month oral administration.

Observation	Males					Females				
	0	24	48	96	192	0	24	48	96	192
Dose (mg/kg)										
n =	10	10	10	10	10	10	10	10	10	10
Stomach	0	0	0	0	1	0	0	0	0	0
- altered content, black										
Lg Intest. - distension	0	0	0	0	3	0	0	0	1	3
Kidney - discoloration, pale and/or tan	0	0	0	1	3	0	0	0	0	4
Uterus - small						0	0	0	0	3

Histopathology: Histological findings are summarized in Table 9. The primary findings were ubiquitous indicators of systemic phospholipidosis and included vacuolation, atrophy, necrosis and inflammatory cell infiltration. Findings were generally of greatest incidence and severity at the highest SCH 34117 dose.

Histopathology	Males					Females				
	0	24	48	96	192	0	24	48	96	192
granulomatous mild	0	0	0	0	1	0	0	0	0	0
Harderian glands	10	10	10	10	10	10	10	10	10	10
Pigment accumulation										
Minimal	0	0	0	3	0	0	0	3	0	0
Mild	0	0	2	5	5	0	0	2	9	5
Moderate	0	0	0	0	2	0	0	0	0	5
Cellular infiltration, macrophage										
Minimal	0	0	0	0	0	0	0	0	0	1
Stomach	10	0	0	10	10	10	0	10	10	10
Vacuolation, epithelium										
Minimal	0			0	4	0		0	3	3
Mild	0			0	3	0		0	0	4
Cellular infiltration, granulomatous										
Minimal	0			0	0	0		0	0	1
Single cell necrosis, epithelium										
Minimal	0			0	1	0		0	0	1
Small intestine	10	0	10	10	10	10	0	10	10	10
Vacuolation, lymphoid nodule, macrophage										
Minimal	0		0	0	0	0		0	0	1
Vacuolation, lamina propria, macrophage										
Minimal	0		0	2	6	0		0	0	4
Mild	0		0	0	3	0		0	0	5
Vacuolation, epithelium										
Minimal	0		0	3	6	0		0	6	9
Spleen	10	0	10	10	10	10	0	10	10	10
Vacuolation, m-phage										
Minimal	0		0	0	5	0		0	0	8
Mild	0		0	0	3	0		0	0	1
Necrosis, lymphoid										
Minimal	0		0	0	2	0		0	0	5
Mild	0		0	0	0	0		0	0	2
Depletion, lymphoid										
Minimal	0		0	3	4	0		0	0	6
Mild	0		0	0	4	0		0	0	2
Moderate	0		0	0	2	0		0	0	0
Testes	10	0	0	10	7					
Cellular debris, spermatic										
Minimal	2			0	4					
Thyroid	10	0	10	10	10	10	0	10	10	10
Vacuolation										
Minimal	0		0	1	3	0		0	0	5
Mild	0		0	0	1	0		0	0	4
Moderate	0		0	0	2	0		0	0	0
Thymus	10	0	10	9	10	10	0	0	10	10
Vacuolation, m-phage										
Minimal	0		0	0	4	0		0	0	3

Histopathology	Males					Females				
	0	24	48	96	192	0	24	48	96	192
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
Mild	0		0	0	2	0			0	2
Necrosis, lymphoid										
Minimal	0		0	1	2	0			0	3
Mild	0		0	0	4	0			0	2
Moderate	0		0	0	0	0			0	1
Depletion, lymphoid										
Minimal	0		0	0	2	0			0	2
Mild	0		0	0	1	0			0	0
Moderate	0		0	0	2	0			1	1
Tongue	10	0	0	10	10	10	0	0	10	10
Vacuolation, myofiber										
Minimal	0			0	3	0			0	4
Mild	0			0	7	0			0	5
Moderate	0			0	0	0			0	1
Trachea	10	0	10	10	10	10	0	10	10	10
Vacuolation, epithelium										
Minimal	0		0	9	1	0		0	7	0
Mild	0		0	0	7	0		0	0	7
Moderate	0		0	0	2	0		0	0	3
Uterus						10	10	10	10	10
Vacuolation, epithelium, endometrium										
Minimal						0	0	0	0	9
Mild						0	0	0	0	1
Vacuolation, endometrium-phage										
Minimal						0	0	0	0	4
Mild						0	0	0	0	4
Moderate						0	0	0	0	1
Atrophy										
Minimal						0	0	0	0	4
Mild						0	0	0	0	1
Urinary bladder	10	0	10	10	10	10	0	0	9	10
Vacuolation, epithelium										
Minimal	0		0	6	1	0		0	0	4
Mild	0		0	0	9	0		0	0	6
Vagina						10	0	0	10	10
Vacuolation, epithelium, cervix										
Mild						0			0	10
Ectasia, gland, clitoris mild										
mild						0			0	1
Mammary glands						10	0	0	10	10
Vacuolation										
Minimal						0			0	1
Mild						0			0	2
Moderate						0			0	1

This study was performed in order to determine doses in a 2 year Phase 4 mouse carcinogenicity study. An MTD of 48 mg/kg was selected in males due to systemic phospholipidosis at this dose and a significant reduction of body weight gain as well as kidney necrosis associated with systemic phospholipidosis at the next highest dose of 96 mg/kg. The MTD for females appears to be 96 mg/kg due to systemic phospholipidosis at this dose and findings of necrosis associated with systemic phospholipidosis and a significant reduction in body weight gain at the next highest dose of 192 mg/kg.

GENETIC TOXICOLOGY:

Bacterial Mutagenicity Study of SCH 45581

Report No.: P-6609 *Study No.:* 99298 *Volume:* 44.11

Study endpoint: Mutagenicity
Study Dates: Starting date 2/17/2000; report issued 5/23/2000
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 45581 (Batch 76214-141-4) diluted in DMSO
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

Methods: SCH 45581 (3-hydroxy-desloratadine), a metabolite of SCH 34117, was assayed in 5 Salmonella tester strains and 1 E. coli strains ± metabolic activation by Aroclor 1254-induced rat liver S9 fraction. The following strains and positive controls were used in 2 plate incorporation tests:

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

SCH 45581 and positive controls were dissolved in DMSO. Doses for Trial 1 were selected based upon results of a previous bacterial mutagenicity study with SCH 34117 and the two mutagenicity assays were conducted at the following concentrations:

Bacterial strain	Phase	Trial 1 Doses ($\mu\text{g}/\text{plate}$)	Trial 2 Doses ($\mu\text{g}/\text{plate}$)	Trial 3 Doses ($\mu\text{g}/\text{plate}$)
TA 1535	nonactivation	94, 188, 375, 750, 1500	63,125,250, 500, 1000	16, 31, 63,125,250, 500
TA 97A	nonactivation	12, 23, 47, 94, 188	4, 8, 16, 31, 63	4, 8, 16, 31, 63, 125
TA 98	nonactivation	47, 94, 188, 375, 750	31, 63, 125, 250, 500	
TA 100	nonactivation	23, 47, 94, 188, 375	16, 31, 63, 125, 250	
TA 102	nonactivation	23, 47, 94, 188, 375	16, 31, 63, 125, 250	4, 8, 16, 31, 63, 125
WP2uvrA	nonactivation	94, 188, 375, 750, 1500	125, 250, 500, 1000, 2000	
TA 1535	activation	94, 188, 375, 750, 1500	63,125,250, 500, 1000	
TA 97A	activation	12, 23, 47, 94, 188	8, 16, 31, 63, 125	
TA 98	activation	47, 94, 188, 375, 750	31, 63, 125, 250, 500	
TA 100, TA 102	activation	23, 47, 94, 188, 375	31, 63, 125, 250, 500	
WP2uvrA	activation	94, 188, 375, 750, 1500	125, 250, 500, 1000, 2000	

The experiments were performed using triplicate plates at each concentration incubated for 48 hours \pm S9. Cytotoxicity was evaluated based on a reduction in revertant colony counts by \sim 30%, inhibition of background bacterial lawn growth and “additional factors based on scientific judgment”. Tests were valid if overnight bacterial cultures reached a density of at least 5×10^8 cells/ml for *Salmonella typhimurium* strain, and approximately 15×10^8 cells/ml for *E. coli*, the mean number of spontaneous revertant colonies/plate was within the range of the historical solvent control values of the same strain, the mean number of induced revertants/plate in the positive controls was at least three-fold greater than the mean of its concurrent solvent control for TA 1535 and at least two-fold greater than the mean of their respective concurrent controls for *E. coli* and other *Salmonella* strains, and at least three doses with revertants are required for data evaluation for each trial. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in at least one of the six tester strains. The magnitude of increase was at least two-fold above the solvent control for strains TA 97A, TA 98, TA 100, TA 102 and WP2uvrA, and three-fold above the solvent control for strain TA 1535. In addition, a dose-response increase of revertant counts in treated plates above that of the solvent control was observed in at least two dose levels, and the increases were reproducible in independent trials.

Results: In the first mutagenicity trial, SCH 45581 did not increase revertant colony counts, \pm S9 activation. Positive controls significantly increased the number of revertant colonies. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 23 $\mu\text{g}/\text{plate}$ and above for TA 97a, 94 and 375 $\mu\text{g}/\text{plate}$ for TA 102, and at 750 $\mu\text{g}/\text{plate}$ and above for TA 1535. Microcolonies were observed at 188 $\mu\text{g}/\text{plate}$ for TA 102, at 375 $\mu\text{g}/\text{plate}$ for TA 1535 and TA 100, at 188, 375 and 750 $\mu\text{g}/\text{plate}$ for TA 98, and at 1500 $\mu\text{g}/\text{plate}$ for WP2uvrA. Cytotoxicity to background lawn was observed at 375 $\mu\text{g}/\text{plate}$ and above for TA 1535, at 188 $\mu\text{g}/\text{plate}$ for TA97a and TA 98, at 188 $\mu\text{g}/\text{plate}$ and above for TA 100, at 94 $\mu\text{g}/\text{plate}$ and above for TA 102 and at 1500 $\mu\text{g}/\text{plate}$ for WP2uvrA. In the activation phase, cytotoxicity to revertant colonies was observed at 23 $\mu\text{g}/\text{plate}$ and above for TA 97a, 188 $\mu\text{g}/\text{plate}$ and above for TA 102, 375 $\mu\text{g}/\text{plate}$ for TA 100, 750 $\mu\text{g}/\text{plate}$ and above for TA 1535, and at 1500 $\mu\text{g}/\text{plate}$ and above for WP2uvrA. Microcolonies were observed at 750 $\mu\text{g}/\text{plate}$ for TA 98 and cytotoxicity to background lawn was observed at 375 $\mu\text{g}/\text{plate}$ for both TA 100 and TA 102, at 750 $\mu\text{g}/\text{plate}$ and above for TA 1535, and at 750 $\mu\text{g}/\text{plate}$ for TA 98.

SCH 45581 did not increase revertant colony counts, \pm S9 activation, in the second trial. However, the revertant counts in strain TA 97a were below historical control levels and were repeated in Trial 3. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 16 μ g/plate and above for TA 97a, 63 μ g/plate for TA 100, 125 μ g/plate for TA 98, and at 500 μ g/plate and above for TA 1535 and WP2uvrA. Microcolonies were observed at 63 and 125 μ g/plate for TA 102, at 125 and 250 μ g/plate for TA 1535, at 250 μ g/plate and above for TA 98, and at 125 μ g/plate and above for TA 100. Cytotoxicity to background lawn was observed at 16 μ g/plate and above for TA 98, at 63 μ g/plate and above for TA 1535, at 125 μ g/plate and above for TA 100, at 250 μ g/plate and above for TA 98 and at 2000 μ g/plate for WP2uvrA. Strains TA 1535 and 102 were repeated in Trail 3 due to cytotoxicity at all doses tested. In the activation phase, cytotoxicity to revertant colonies was observed at 31 μ g/plate and above for TA 97a, 250 μ g/plate and above for TA 100 and 102, 500 μ g/plate for TA 98, and at 1000 μ g/plate and above for WP2uvrA. Microcolonies were observed at 500 μ g/plate for TA 98 and at 1000 μ g/plate for TA 1535. Cytotoxicity to background lawn was observed at 500 μ g/plate for both TA 100 and TA 98, at 1000 μ g/plate for TA 1535, and at 2000 μ g/plate for WP2uvrA.

In the third trial, SCH 45581 did not increase revertant colony counts without activation in strains TA 97a, TA 102 and TA 1535. Cytotoxicity to revertant colonies was observed at 31 μ g/plate and above for TA 97a, and at 125 μ g/plate for TA 102. Microcolonies were observed at 500 μ g/plate for TA 1535. Cytotoxicity to background lawn was observed at 125 μ g/plate for both TA 97a and 102, and at 250 μ g/plate and above for TA 1535.

Thus, SCH 45581, up to 1000 μ g/plate in *Salmonella* strains and up to 2000 μ g/plate in *E. coli*, was negative in the bacterial mutation test (Ames assay) using plate incorporation, in concurrence with the sponsor's conclusion.

Mouse bone marrow erythrocyte micronucleus study of SCH 45581

Schering Study No.: 99539 *Volume:* 44.11

Study endpoint: Clastogenicity
Study Dates: Starting date 12/13/1999; report issued 5/22/2000
Testing Lab: Schering Plough Research Institute, Lafayette, NJ
Test Article: SCH 45581 (Batch No. 75669-17) in 0.4% methylcellulose
GLP: The study was accompanied by a signed GLP compliance statement.
QA report: Yes.

Methods: SCH 45581 was evaluated for its potential to induce micronuclei in the bone marrow of male and female CD-1 [ICR]BR VAF/Plus mice (6 weeks old; 19.6-31.9 g; 6/sex/dose/sacrifice time) following two consecutive daily IP doses of 10, 20 or 40 mg/kg (dose volume: 10 ml/kg; concentrations: mg/ml). Dose selection was based upon dose-ranging studies. In the first study excessive mortality was observed following a single IP doses of 125-2000 mg/kg (10 ml/kg). In the second study, mice were administered two consecutive daily IP doses of 6.25, 12.5, 25, 50 and 100 mg/kg. Mortality was observed at doses of 50 and 100 mg/kg in males and at the high dose in females. The PCE/NCE ratio was reduced by 19 and 61% at doses

of 25 and 50 mg/kg, respectively, in males and 18 and 53%, respectively, in females. Adverse clinical signs included rough hair coat and hypoactivity at doses of 50 mg/kg and greater.

Two definitive micronucleus trials were performed and mice were sacrificed at 24 hours after the final dose in the first trial and 48 hours after final dose administration in the second trial; animals treated with positive control were sacrificed at 24 and 48 hours after dosing in trials 1 and 2, respectively. Bone marrow erythrocytes were removed from the femur of five mice from each dose group/sex and two bone marrow smears were prepared for each mouse. A total of 2000 polychromatic erythrocytes (PCE) for each mouse were screened for micronuclei. The micronucleus frequency of each dose for each sex was calculated from the total number of micronucleated PCE in 10000 PCE pooled from five mice and compared with that of the vehicle control. Micronucleated NCE were evaluated during the screening of micronuclei in 2000 PCE for each mouse and the total number was estimated based upon PCE/NCE ratio. Bone marrow toxicity was evaluated by the PCE/NCE ratio which was determined by the number of NCE enumerated during scoring approximately the first 200 PCE in each mouse. A trial was considered to be valid if the micronucleus frequency in vehicle controls was in the normal range (0.08 to 0.5%); a significant increase of micronucleus frequency in the positive control group above the vehicle control group; and data were available from at least three mice from the vehicle and positive control groups and from each test article dose group. The test article was considered to have caused a positive response if the test article induces a statistically significant increase of micronucleus frequencies in PCE at two consecutive doses. Cyclophosphamide (50 and 30 mg/kg for Trial 1 and 2, respectively) was used as a positive control.

Results: There was no significant increase in micronucleus frequency at any dose in males or females. Clinical signs were observed in high-dose animals (rough hair coat). In trial one, dose-related bone marrow toxicity was observed (9, 12 and 33% decrease in PCE/NCE ratios in males and 11, 14 and 24% in females at the low-, mid- and high-doses, respectively). At 48 hours, bone marrow toxicity was noted in mid- and high-dose males and females (11-12% and 23-36% reduction in PCE/NCE ratio, respectively). Cyclophosphamide induced a 16-fold and 6-fold increase of micronucleus frequency over the vehicle controls in trials one and two, respectively. The results indicate that SCH 45581 was negative under the conditions of this micronucleus assay, in concurrence with the sponsor's conclusion. However, the high-dose of 40 mg/kg appears to be low, especially in females, since no significant toxicity was observed in the definitive trials and since mortality in females was observed only at doses of 100 mg/kg or greater in the dose-ranging trials.

OVERALL SUMMARY AND EVALUATION:

Multiple Dose Toxicology: A 3 month oral (dietary admixture) dose-ranging study in mice (24, 48, 96 and 192 mg/kg) was performed for the purpose of dose selection for a Phase 4, 2 year mouse carcinogenicity study. Drug-related mortality was observed in two high-dose males. Mean body weight gain was reduced by greater than 10% in the three highest dose-groups in males (high-dose males lost weight) and in high-dose females. The primary histological findings were

indicative of systemic phospholipidosis (vacuolation, atrophy, necrosis, cellular inflammation) and were found in organs and tissues throughout the body including the brain, epididymides, heart, kidneys, liver, lungs, ovaries, seminal vesicles, stomach, spleen, thyroid, thymus, uterus, urinary bladder, and vagina. Histologic findings in the liver, lung, thymus and uterus were associated with significant changes in absolute or relative organ weight. Other significant findings included increased levels of BUN, AST, ALT and AP which were associated with histologic changes. In addition, induction of cytochrome P-450 in females and the enzymes EROD (2 highest doses) and PROD (3 lowest doses) as well as Cyp 2B1/2 (males and females) and Cyp 1A2 and P450 A (males only) were noted. An MTD of 48 mg/kg was identified in males and 96 mg/kg was selected in females. The toxicity profile is comparable to that observed previously in rats and monkeys.

Genetic Toxicology: An *in vivo* mouse bone marrow micronucleus assay and an Ames assay were performed with SCH 45581 (the 3-hydroxy metabolite of SCH 34117). Both assays were negative although high dose selection in the former study could likely have been increased. The results are consistent with the genotoxicity battery performed with SCH 34117.

RECOMMENDATIONS

1. High doses of 48 mg/kg in males and 96 mg/kg in females in the 2 year mouse carcinogenicity study are recommended due to significant reductions in body weight gain and systemic findings of vacuolation and necrosis at the next higher doses in the 3 month dose-ranging study in mice.
2. The low and mid-doses in males should be lowered to 4 and 16 mg/kg, respectively, to provide an adequate dose response for the high dose. Similarly, the low and mid-doses in females should be increased to 10 and 32 mg/kg, respectively.
3. The above recommendations are pending the CAC's concurrence.

Timothy J. McGovern, Ph.D., Pharmacologist

Addendum 1: Histopathology inventory for SCH 34117.

IND 55,364

CC:

HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/R. Nicklas
HFD-570/G. Trout
HFD-570/T.J. McGovern
HFD-540/B. Hill

Addendum 1: Histopathology inventory for IND 55,364.

* Organ weight obtained

Study No.	P-6526	D18289	SN 98088	P-6973	P-6527	SN 98089	P-6976	SN 97253
Duration	14-day	14-day	28-day	3-month	14-day	28-day	3-month	3-month
Species	rat	rat	rat	Rat	monkey	monkey	monkey	mouse
Adrenals	X*		X*	X*	X*	X*	X*	X
Aorta	X		X	X	X	X	X	X
Bone marrow smear	X		X	X	X		X	X
Bone (femur)	X		X	X	X	X	X	X
Bone (rib)					X	X		
Bone (strenum)	X		X		X	X		
Brain:	X*		X*	X*	X*	X*	X*	X*
Cecum	X		X		X	X		
Cervix			X					
Colon	X		X		X	X		
Duodenum	X		X	X	X	X	X	
Epididymis	X*		X*	X*	X*	X	X*	X*
Esophagus	X		X	X	X	X	X	X
Eye	X		X	X	X	X	X	X
Fallopian tube								
Fat								
Gall bladder					X	X	X	X
Gross lesions	X	X			X	X	X	X
Harderian gland	X		X	X				X
Heart	X*		X*	X*	X*	X*	X*	X*
Hyphophysis								
Ileum	X		X	X	X	X	X	
Injection site	NA	NA	NA		NA	NA		
Jejunum	X		X	X	X	X	X	
Kidneys	X*	X*	X*	X*	X*	X*	X*	X*
Lacrimal gland					X	X	X	
Larynx								
Liver	X*	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X*	X*	X*
Lymph nodes, cervical								X
Lymph nodes (LALN)				X			X	
Lymph nodes, mandibular	X		X		X	X		X
Lymph nodes, mediastinalis								
Lymph nodes, mesenteric	X		X		X	X		X
Mammary gland	X		X	X	X	X		X
Nasal cavity								
Optic nerves			X					
Ovaries	X*		X*	X*	X*	X*	X*	X*
Oviduct								
Pancreas	X	X	X	X	X	X	X	X
Parathyroid	X		X	X	X	X	X	X
Peripheral nerve				X				X
Pharynx								
Pituitary	X*		X*	X*	X*	X*	X*	X
Prostate	X*		X*	X*	X*	X*	X*	X
Rectum								
Salivary gland	X*		X*	X*	X*	X*	X*	X*
Sciatic nerve	X		X		X	X		
Seminal vesicles	X		X	X	X	X	X	X
Skeletal muscle	X		X	X	X	X	X	X
Skin	X		X	X	X	X	X	X
Spinal cord	X		X	X	X	X	X	X
Spleen	X*		X*	X*	X*	X*	X*	X*
Stomach	X		X	X	X	X	X	X
Testes	X*		X*	X*	X*	X*	X*	X*
Thoracic Limb	X							
Thymus	X*		X*	X*	X*	X*	X*	X*
Thyroid	X*		X*	X*	X*	X*	X*	X
Tongue	X		X	X	X	X	X	X
Trachea	X		X	X	X	X	X	X
Urinary bladder	X		X	X	X	X	X	X
Uterus	X*		X*	X*	X*	X*	X*	X*
Uterine horn								
Vagina	X		X	X	X	X	X	X

**HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**

Review #5

IND No. 55,364 **Serial No.** 051 **Submission Date:** 26 APR 1999
094 01 NOV 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 07 JUN
2000

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

Sponsor: Schering Corporation, Kenilworth, NJ

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

Class: Anti-histamine

Indication: Seasonal allergic rhinitis

Route of Administration: Oral (tablet)

Proposed Clinical Protocols: None with these submissions.

Previous Clinical Experience: Phase I, II and III studies in both healthy volunteers and patients with seasonal allergic rhinitis.

Previous Review(s), Date(s) and Reviewer(s):

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998
Review #4	April 1 – October 5, 1999	McGovern	January 31, 2000

The following table summarizes the studies submitted and reviewed in this document:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Serial #
Safety Pharmacology:		
Effect of loratadine and its metabolite, descarboethoxyloratadine, on the QT interval in the isolated perfused rabbit heart model (Langendorff)	30523	051
Effect of IN-0133 on electrophysiological and mechanical properties of guinea pig ventricular muscle	30416	051
Effects of IN 0132 on the Na ⁺ current in rabbit ventricular myocytes	30417	051
Report on the effect of IN-0132, IN-0133, 0049 and IN-0057 on two K currents, iKr and iKl in rabbit ventricular myocytes	30148	051
Pharmacokinetics:		
SCH 34117: A study of the tissue distribution of radioactivity in male and female sprague dawley rats and male long evans rats following a single oral dose of ¹⁴ C-SCH 34117	P-6741	094

Studies Not Reviewed in this IND: Study P-6943 (Serial # 094): “SCH 34117: Vehicle for intravenous delivery of SCH 34117: (Solubility testing, in-life compatibility and stability” was not reviewed. Both 0.1 M citric acid in saline and 40% aqueous HPbCD (pH 6.01) were suitable vehicles for SCH 34117 at a concentration of 6.5 mg/ml. Rats did not exhibit adverse reactions to either vehicle following a single intravenous administration of 1 ml/kg. ¹⁴C-SCH 34117 was stable in both vehicles for 24 hours in the dark at room temperature and/or at 4 degrees Celsius and in 0.1 M citric acid in saline at room temperature for up to 8 days. The sponsor concludes that 0.1 M citric acid in saline will be used for IV administration of ¹⁴C-SCH 34117.

Studies Previously Reviewed: None

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

SAFETY PHARMACOLOGY: The sponsor submitted four reports which assessed the comparative potential to induce adverse cardiac events of SCH 34117 and loratadine; results of these studies are summarized in Table 1. SCH 34117 increased QT interval (up to 41% at 10 μM) in a dose- and time-dependent manner in isolated rabbit hearts, primarily due to increasing the QRS complex (up to 5-6-fold at 10 μM). SCH 34117 alone did not affect JT interval but enhanced a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at concentrations up to 50 μM. In isolated perfused guinea pig left ventricular papillary muscle, SCH 34117 decreased Vmax and velocity of impulse conduction and increased excitation threshold (≥ 30 μM) while producing a negative inotropic effect (10 μM). 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) to ~ ½ control value at 6 x 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. Thus, SCH 34117 exerted effects on various cardiac parameters at concentrations ranging from 5-100 µM.

Table 1. Safety pharmacology studies demonstrating cardiac effects of SCH 34117.

Parameter/Model	Activity
Isolated, perfused rabbit hearts	<p>SCH 34117: increased QT interval (15% and 41% at 5 µM and 10 µM, respectively, after 30 minutes); experiments prematurely terminated after 50 µM due to sustained ventricular fibrillation; NOEL = 1 µM.</p> <p>QT increase at 10 µM increased through first 100 minutes; could not be measured after 2 hours due to flattening of T wave;</p> <p>QRS interval increased 5 to 6-fold at 10 µM 2 hours after dosing; increased up to 34% at 0.5 µM after 3 hours; NOEL = 0.2 µM.</p> <p>No effect of SCH 34117 alone on JT interval. Produced nearly two-fold increase in JT interval at 0.5 µM in combination with quinidine compared to quinidine alone (15%).</p> <p>Loratadine (up to 50 µM) had no effect on QT, QRS or JT intervals</p>
Perfused guinea pig left ventricular papillary muscle	<p>Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.</p> <p>No effect on resting potential or action potential duration at drug concentration of 10, 30 or 100 µM.</p> <p>SCH 34117 decreased Vmax at ≥ 30 µM with pacing at 1 Hz; decrease of 57% at 100 µM. Associated with decrease in velocity of impulse conduction and increase in excitation threshold. Decrease in Vmax enhanced at higher pacing frequencies. Full reversibility not obtained up to 2 hrs.</p> <p>Negative inotropic effect in 4 of 5 preparations at 10 µM (decreased isometric force to 70% of pre-drug level at 1 Hz).</p>
Isolated rabbit ventricular myocytes	<p>Remark: Drug listed in report as IN-0133, assumed to be SCH 34117. Drug listed in report as IN 0132, assumed to be Loratadine.</p> <p>Effects on Na⁺ current: SCH 34117 (100 µM; 5-10 min) reduced Na⁺ current at holding potentials of -100 to -80 mV more effectively than 100 µM loratadine. Loratadine showed preferential binding to channel in inactivated state.</p> <p>Effects on delayed rectifier current (iKr): SCH 34117 (6×10^{-6} M) reduced iKr current to ~ ½ control value at 10 mV. Only small remnant of iKr current visible at 3×10^{-5} M. Concentration at which ½ current is blocked (k0.5) = 5×10^{-6} M. k0.5 for loratadine = 8.7×10^{-6} M</p> <p>Effect on inward rectifier current (iK1): no effect at 10^{-5} M; IV curve flatter at 3×10^{-5} M. Loratadine had more pronounced effect than SCH 34117 and was more slowly reversible.</p>

PHARMACOKINETICS AND TOXICOKINETICS:

Pharmacokinetic parameters in rats following oral (gavage) administration are summarized in Table 2. The C_{max} and AUC for total radioactivity were 1.5-1.8 times higher in males. Plasma concentrations of unchanged drug at 3 hours were 2.6 times higher in females than in males. The plasma concentrations < LOQ (0.5 ng/ml) by 24 hours in males and 72 hours in females. The AUC for SCH 34117 was not calculated since the concentration fell below the LOQ before adequate elimination phase could be described.

Table 2. PK values following single oral dose of SCH 34117 (6.5 mg/kg) in SD rats.

Parameter	Males	Females
	Drug-derived radioactivity	
C _{max} (µg equiv/g)	0.648	0.426
T _{max} (hr)	6	3
AUC(tf) (µg equiv.hr/g)	13.9	7.65
	SCH 34117	
C _{max} (µg/ml)	0.0995	0.259
T _{max} (hr)	3	3
AUC(tf) (µg equiv.hr/g)	Not calculated	Not calculated

Previously submitted 14-day and 3-month studies in rats have demonstrated similar findings at comparable doses including increased SCH 34117 exposure in females.

Distribution: Table 3 summarizes the tissue distribution of a single oral (gavage) dose of ¹⁴C-SCH 34117 (6.5 mg/kg) in Sprague Dawley rats. In males, tissues (excluding GI tract) with the highest concentrations of radioactivity (6 hours) were the pituitary, adrenal gland, lung, liver, and mesenteric lymph nodes. At 168 hr post-dose the concentration of radioactivity in most tissues was about 1- to 12-fold greater than those in plasma and the tissue to plasma ratios were generally higher than those at 6 hours. At 672 hours post-dose 0.071% of administered dose was in collected tissues and only thyroid had notable concentrations (consistent with loratadine studies). Females were similar to males in terms of tissue distribution and brown fat, peritoneal fat kidneys and thyroid concentrations were higher than plasma at 168 hours and only 0.002% of administered dose was noted in collected tissues. The tissues with lowest concentrations were the plasma, brain, blood, eyes, spinal cord, and testes. The results suggest a greater penetration of drug-derived radioactivity into tissues in female rats compared to males as mean plasma concentrations were 2- to 4-fold higher from 1 to 6 hours and radioactivity concentrations in many tissues in females at 1, 3 and 6 hours post-dose were approximately 1.5- to 2.5-fold greater in comparison to males.

Table 3. Tissue distribution of ¹⁴C-SCH 34117 in rats after single oral gavage administration.

Tissue	Males (6 hrs)		Females (3 hrs)	
	Total radioactivity (µg equiv/g)	Tissue:Plasma ratio	Total radioactivity (µg equiv/g)	Radioactivity in peptide fraction
Plasma	0.648	1	0.426	1
Adrenal gland	17.7	27.2	30.2	70.9
Harderian gland	10.2	15.7	11.7	27.5
Kidney	7.90	12.2	13.3	31.2
Liver	15.4	23.8	20	46.9
Lungs	15.5	23.9	28.4	66.7
Mes. Lymph nodes	12	18.5	11.9	27.9
Pituitary	30.4	46.9	31.8	74.6
Spleen	8.17	12.6	14.7	34.5
Thyroid	8.44	13	14.3	33.6

In male Long Evans rat there was no difference in binding of radioactivity to pigmented or non-pigmented skin following a single oral gavage dose (6.5 mg/kg; Table 4). The eye had concentrations ranging from 1.43 to 4.81 µg equiv/g which declined slowly and were still detectable at 672 hours. The highest concentrations were detected in the liver and kidneys.

Table 4. Tissue distribution in male Long Evans rats after single oral gavage administration.

Tissue	Males (3 hrs)	
	Total radioactivity (µg equiv/g)	Tissue:Plasma ratio
Plasma	0.795	1
Blood	0.875	1.1
Eyes (pigmented)	3.57	4.49
Kidney	9.27	11.7
Liver	26	32.7
Skin (non-pigmented)	1.58	1.99
Skin (pigmented)	1.72	2.16

Excretion: Following a single oral dose of ¹⁴C-SCH 34117 to Sprague Dawley rats, 98 and 95% of administered radioactivity was recovered by 168 hours from males and females, respectively. 69-70% of the dose was recovered in feces while 25-27% was eliminated in urine. Negligible amounts were recovered in cage wash and as CO₂ (0.06-0.36%).

OVERALL SUMMARY AND EVALUATION

Safety Pharmacology: 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 did enhance a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50 μM . SCH 34117 also decreased V_{max} and velocity of impulse conduction and increased excitation threshold ($\geq 30 \mu\text{M}$) 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 (i_{Kr}) current to $\sim 1/2$ control value at $6 \times 10^{-6} \text{ M}$ as the concentration at which $1/2$ current is blocked ($k_{0.5}$) was $5 \times 10^{-6} \text{ M}$ ($k_{0.5}$ for loratadine was 8.7×10^{-6}). SCH 34117 had no effect at 10^{-5} M on inward rectifier current (i_{K1}) although the curve was flatter at $3 \times 10^{-5} \text{ M}$; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters in vitro at concentrations ranging from 5-100 μM . SCH 34117 was previously 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. In addition, the absence of loratadine-induced adverse cardiac effects in humans suggests that SCH 34117 is reasonably safe in this regard. A previous consult with Dr. Peter Honig, acting Medical Officer, concluded that no further preclinical assessment of cardiovascular effects is necessary.

Pharmacokinetics: The C_{max} and AUC for total radioactivity following oral gavage administration were 1.5-1.8 times higher in males compared to females. However, plasma concentrations of unchanged drug was 2.6 times greater in females at 3 hours after dosing. Plasma concentrations were less than the LOQ by 24 hours in male and 72 hours in female. Tissue distribution of a single oral (gavage) dose of ^{14}C -SCH 34117 in Sprague Dawley rats was observed primarily in the pituitary, adrenal gland, lung, liver, spleen and mesenteric lymph nodes. At 168 hr post-dose the concentration of radioactivity in most tissues was about 1- to 12-fold greater than those in plasma and the tissue to plasma ratios were generally higher than those at 6 hours. At 672 hours post-dose 0.071% of administered dose was in collected tissues and only thyroid had notable concentrations (consistent with loratadine studies). The results suggest a greater penetration of drug-derived radioactivity into tissues in female rats compared to males as mean plasma concentrations were 2- to 4-fold higher from 1 to 6 hours and radioactivity concentrations in many tissues in females at 1, 3 and 6 hours post-dose were approximately 1.5- to 2.5-fold greater in comparison to males. Tissue distribution of SCH 34117 is comparable to that observed during the loratadine development program. No difference in tissue distribution to pigmented or non-pigmented skin was noted in male Long Evans rats although radioactivity was detected in the eye. A single oral gavage dose of ^{14}C -SCH 34117 was excreted primarily in feces.

RECOMMENDATION

None at this time.

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND 55,364

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HFD-570/G. Trout
HFD-570/T.J. McGovern

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

Review #4

IND No. 55,364	Serial No. 048	Submission Date: 01 APR 1999
	075	13 AUG 1999
	084	17 SEP 1999
	088	05 OCT 1999

Reviewer: Timothy J. McGovern, Ph.D.
2000

Review Completed: 31 JAN

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

Sponsor: Schering-Plough Corporation

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

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Route of Administration: Oral (tablet)

Proposed Clinical Protocols: None with these submissions.

Previous Clinical Experience: Phase I and Phase II studies in both healthy volunteers and patients with seasonal allergic rhinitis.

Previous Review(s), Date(s) and Reviewer(s):

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998

Background: The submission of Serial No 048 contains summary reports of 3-month oral (gavage) toxicity studies in rats and monkeys (Study # P-6973 and P-6976, respectively). The sponsor previously submitted draft tables of clinical observations and gross findings from a 3-month monkey study (Serial No 032) in order to gain Agency concurrence on the Sponsor's plan not to perform an additional 3-month study in monkeys to fulfill bridging requirements to the chronic studies performed in the development program for loratadine. The sponsor was informed that a final decision on this issue must await submission of the histopathology and PK/TK data

from the 3-month monkey study (see Review #3). The sponsor's intent with the current submissions is to submit supporting toxicology information for planned chronic idiopathic urticaria trials which will be six weeks in duration and are planned to start in late April, 1999, to support bridging to the chronic toxicology program performed with loratadine and to obtain a waiver for carcinogenicity studies assessing SCH 34117. Currently, trials up to 4 weeks in duration have been performed based upon summary reports of 4-week toxicology studies in rats and monkeys. A Pre-NDA meeting was held May 11, 1999 to discuss, among other issues, the use of the 3-month studies to bridge to the chronic loratadine development program. Submission 075 contains the sponsor's request for a waiver from performing carcinogenicity studies in support of the desloratadine bridging strategy and includes the in vivo mouse micronucleus assay. Submission 088 includes additional information in support of the carcinogenicity waiver request. Submission 084 includes the final 3-month toxicology study reports including toxicokinetic data.

The issue regarding the carcinogenicity waiver request was addressed by the Senior Pharmacology/Toxicology Policy Group on September 14, 1999. The background packages provided to the Policy Group and the minutes of the Policy Group meeting are included as Attachments 1, 2 and 3 at the end of this review. See the minutes of the Policy Group meeting for the final recommendations regarding the sponsor's waiver request.

The following table summarizes the studies submitted in these submissions:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Serial #	Volume
Multiple Dose Toxicology:			
Summary report of 3-mos oral (gavage) rat toxicology study	P-6973	048	12.1
Summary report of 3-mos oral (gavage) monkey toxicology study	P-6976	048	12.2
Final report of 3-mos oral (gavage) rat toxicology study	P-6973	084	23.1
Final report of 3-mos oral (gavage) monkey toxicology study	P-6976	084	23.4
Genetic Toxicology:			
Mouse bone marrow erythrocyte micronucleus study of SCH 34117	P6912	075	21.7

Studies Not Reviewed in this IND: None.

Studies Previously Reviewed: None

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

TOXICOLOGY

MULTIPLE-DOSE TOXICITY:

Rat, 3-Month Oral (Gavage) Toxicity

Doc. No.: P-6973 Study No.: N003134B Sponsor Study No.: 97016 Vol.: 23.1

Study Dates: Starting date: 3/9/1998; summary report issued: 7/1999

Testing Lab: _____

Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not reported) in 0.4% methylcellulose; SCH 29851 (Batch MI-A-00851; purity not reported)

Concentration: 0.6-24 mg/ml.

Dose Volume: 5 ml/kg.

GLP: This report included a signed GLP report.

QA report: Yes.

Methods: Sprague-Dawley rats (5-7 weeks old, 169-291 g) were assigned to the following treatment groups:

Dose	Veh.	3	30	60	120	120 mg loratadine/kg/day
(mg SCH 34117/kg/day):	Control					
No./sex	10	10	10	10	10	10

Each rat received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months. The following observations were made:

- Clinical observation . . . assessed daily
- Body weight weekly
- Food consumption weekly
- Water consumption . . . not assessed
- Health exam not assessed
- Ophthalmoscopy pre-test and Week 12; left eye only
- ECG not assessed
- Hematology Weeks 4 and 13
- Clinical chemistry Weeks 4 and 13
- Urinalysis Weeks 4 and 13
- Enzyme induction Liver samples assayed for protein content, cytochrome P450 content, 7-pentoxoresorufin O-dealkylase (PROD) activity and 7-ethoxoresorufin O-dealkylase (EROD)
- Organ weights at sacrifice (for specific tissues/organs see Addendum, page 32)
- Gross pathology at sacrifice
- Histopathology at sacrifice, all tissues were examined in the control (vehicle and comparative) high-mid-dose and high-dose rats (for specific tissues/organs see Addendum, page 32). Target organs were evaluated to the no-effect level in the low- and low-mid-dose groups.

ii blood samples obtained from 2 rats/sex/group/time point from the dosed rats at approximate times of 1, 2.5, 4, 8, 12 and 24 hours after dosing on Days 1 and during week 9.

Results:

Mortality: Mortality was noted following blood collection on Day 1 in all groups except for the low-dose group; vehicle control animals were not bled. The animals that died were replaced. Treatment-related mortality was noted in high-dose males (9 of 10, Days 19-63), in females at doses \geq 30 mg/kg DCL (lower-middle-dose: 2 of 10, days 41 and 68; upper-middle-dose: 6 of 10, days 9-63; high-dose: 10 of 10, days 19-36) and in comparative controls (6 of 10, days 23-87).

Table 1: Total incidence of mortality.

Dose (mg SCH 34117/kg/day):	0	3	30	60	120	120 mg loratadine/kg/day
Males	0	0	0	0	9	0
Females	0	0	2	6	10	6

Clinical Observations: Anti-cholinergic effects were the primary drug-related clinical observations in this study (Table 2). These included enlarged, few or no feces in animals administered doses of \geq 30 mg/kg SCH 34117 and loratadine-treated animals. Increases in the incidence of hypothermia, lethargy, paleness, rough coat, extended abdomen, thin appearance, ataxia, labored respiration/respiratory sounds, wet urogenital region and hunched posture were also noted in these groups. The incidence in the loratadine-control group showed greater similarity to the 60 mg/kg SCH 34117 group than the 120 mg/kg SCH 34117 group, likely due to differences in systemic exposure to SCH 34117.

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Table 2. Clinical observations in rats following 3-month administration.

Observation	Females						Males						
	Dose (mg/kg)	0	3	30	60	120	120 - Lor	0	3	30	60	120	120 - Lor
Feces - few		0	0	8	10	10	10	0	1	1	10	10	7
Feces - none		0	0	0	1	0	3	0	0	0		1	1
Feces - enlarged		0	0	10	9	10	10	0	0	10	10	10	10
Hunched posture		0	0	0	6	10	10	0	1	0	1	10	1
Hypothermic		0	0	0	0	6	0	0	0	0	1	5	0
Lethargic		0	0	0	3	9	2	0	0	0	1	4	3
Pale		0	0	1	7	10	7	0	0	0	1	7	1
Rough coat		0	0	3	9	10	9	0	1	0	1	9	1
Thin appearance		0	1	5	10	10	10	0	1	0	1	8	2
Ataxic		0	0	0	0	1	0	0	0	0	1	2	1
Convulsive		0	0	0	1	0	0	0	0	0	0	1	0
Labored respiration		0	0	2	5	9	5	0	0	1	2	6	0
Nasal discharge - red		0	0	0	0	0	5	0	1	0	2	6	0
Respiratory sounds - rales		0	0	2	3	3	0	0	1	1	0	4	1
Swollen abdomen		0	0	0	0	0	2	0	0	0	0	2	0
Urogenital region - wet		0	0	1	1	7	2	0	0	0	0	1	0

Body Weight: Body weight gain was significantly reduced in upper-mid and high-dose males and females administered ≥ 30 mg/kg (Table 3). In males, significant reductions in the upper-mid and high-dose groups were observed from Days 29 and 8, respectively. In females, significant reductions in the lower-mid, upper-mid and high-dose groups were observed from Days 43, 22 and 36, respectively. The active control groups were also reduced (from Days 22 in males and 29 in females) and were comparable to the upper-mid-dose DCL groups.

Table 3: Change in body weight gain following 3-months treatment.

Dose (mg SCH 34117/kg/day):	3	30	60	120	120 mg Lor/kg/day
Males					
% Δ from control	↓1	↓12	↓33	↓99*	↓30
Females					
% Δ from control	↓7	↓33	↓73	↓139**	↓62

*: Day 54.

** : Day 36.

Food consumption: Food consumption was reduced in male rats administered 60 or 120 mg/kg SCH 34117 beginning on Day 8. The statistically significant reduction in the high dose group (36-54%) was continuous, while that in the 60 mg/kg group was intermittent, ranging from 22% at Day 8 to 9-12% on Days 78-91. Significant reductions in active control males were noted only on Days 8 and 57 (16 and 19%, respectively). Females were more significantly affected as reductions were consistently reported in the same three groups from Day 8 onward. Reductions ranged from 24-32% in the 60 mg/kg group, 36-75% in the 120 mg SCH 34117/kg group, and 13-36% in the loratadine treatment group.

Ophthalmoscopy: No treatment-related findings were reported.

Hematology: The high-dose SCH 34117 groups could be assessed only at Day 23 due to high mortality. Significant, but small, increases in erythrocyte, hemoglobin and hematocrit levels were noted (Table 4). In addition, total leukocyte counts were reduced and platelet counts were increased. WBC differentiation demonstrated reduced lymphocytes and eosinophils. At day 92, findings included a slight reduction in mean corpuscular hemoglobin concentration in active male controls, increased erythrocyte hemoglobin, and increased hematocrit in the two mid-dose female groups and the female active control group. Monocyte reductions were also noted in upper-mid dose and active control males, while prothrombin and activated partial prothrombin time were reduced in males, but increased in females.

Table 4. Hematologic findings in rats following 3-month administration.

Hematology	Males						Females					
	Dose (mg/kg)						Dose (mg/kg)					
	0	3	30	60	120*	120 - L	0	3	30	60	120*	120 - L
Leukocyte												
% Δ from control		↑4	↓4	↑5	↓32	↓7		↑14	0	↑17	↓25	↓13
Erythrocyte												
% Δ from control		↑4	↑2	0	↑16	↑1		↑2	↑10	↑12	↑10	↑13
Hemoglobin												
% Δ from control		↑1	↑2	↓1	↑12	↓3		↑2	↑10	↑11	↑7	↑7
Hematocrit %												
% Δ from control		↑2	↑2	↑1	↑12	0		↑2	↑10	↑12	↑6	↑11
Platelets												
% Δ from control		0	↓14	↑7	↑32	↓1		↓2	↓12	↑8	↑51	↑15
Lymphocytes												
% Δ from control		↑2	0	↑4	↓49	↑6		↑10	↑1	↓5	↓67	↓27
Monocytes												
% Δ from control		↑7	↓64	↓66	↑147	↓70		↑48	↓71	↑176	↑8	↓33
Eosinophils												
% Δ from control		0	↓15	↓20	↓69	↓40		↑38	↓15	↓54	↓79	↓46
Neutrophils												
% Δ from control		↑9	↓4	↑36	↑50	↑50		↑48	↑16	↑170	↑377	↑115
Prothrombin time (seconds)	13	13	12	12	13	11.5	11	11	10.9	11		11.5
APTT (seconds)	12	11	9.7	9.6	9.9	9.4	10	10	9.8	11		11

Shaded areas indicate statistically significant difference from control group ($p < 0.05$).

* Day 23.

Clinical Chemistry: The high-dose SCH 34117 groups were only assessed on Day 23 due to high mortality. Drug-related findings are summarized in Table 5 and include slight alterations in albumin, increases in cholesterol, globulin, and total protein. Aspartate aminotransferase, alanine aminotransferase and BUN were also increased 2.5 to 5-fold, 1 to 2-fold, and 1.5 to 2-fold, respectively, in males and females, while A/G ratio, glucose, and triglycerides were slightly to moderately reduced.

Table 5. Clinical chemistry findings in rats following 3-month administration.

Clinical chemistry	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	3	30	60	120*	120-L	3	30	60	120*	120-L
Albumin % Δ from control	↑5	↑11	↑11	↓12	↑16	↑6	↑4	↓14	↓17	↓12
Cholesterol % Δ from control	↑12	↑26	↑46	↑69	↑12	↑11	↑21	↑66	↑24	↑124
Globulin % Δ from control	no Δ	↑9	↑23	↑15	↑27	↑10	↑15	↑15	↓12	↑35
Total protein % Δ from control	↑5	↑12	↑17	↓3	↑22	↑7	↑7	↓7	↓15	↑1
Aspartate aminotrans % Δ from control	↑2	↓11	↓14	↑489	↓14	↑2	↑22	↑60	↑250	↑32
Alanine aminotrans % Δ from control	↑8	↑11	↑14	↑231	↑25	↑37	↑39	↑16	↑103	↓20
AG ratio % Δ from control	↑2	↓1	↓15	↓21	↓13	↓5	↓8	↓24	↓1	↓37
Glucose % Δ from control	↓6	↓6	↓10	↓51	no Δ	↓5	↓10	↓16	10	↓12
Triglycerides % Δ from control	↑17	↓22	↓72	↓65	↓74	↑10	↑21	↑74	↓51	↓50
BUN % Δ from control	↓7	no Δ	no Δ	↑159	↑14	no Δ	↓6	↑81	↑207	↑88

Shaded areas indicate statistically significant difference from control group (p < 0.05).

120-L: 120 mg/kg loratadine active control group.

* Day 23.

Enzyme Induction: Liver weight, liver to body weight ratio and microsomal protein content were all increased in male rats administered 30 and 60 mg/kg SCH 34117 and 120 mg/kg loratadine (Table 6). The high-dose SCH 34117 groups were not assessed due to the high incidence of mortality. These findings were consistent only in the female active control group. In addition, cytochrome P450 induction was greater in females while induction of PROD was greater in males. Responses tended to be greater in the active control animals compared to the animals administered 60 mg/kg SCH 34117.

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Table 6. Enzyme induction in rats following 3-month drug administration.

Dose (mg/kg/d)	Males					Females				
	0	3	30	60	120-L	0	3	30	60	120-L
Liver weight										
% Δ from control		↓1	↑40	↑39	↑79	↓1	↓9	↑1		↑62
Liver/Body wt ratio										
% Δ from control		no Δ	↑41	↑67	↑111	↑7	↑7	↑41		↑115
Microsomal protein (mg/tot liver)										
% Δ from control		↑21	↑98	↑71	↑102	↓4	↑15	↑36		↑172
Cytochrome P450										
% Δ from control										
Nmol/mg microsomal protein		↓6	↑7	↑9	↑13	no Δ	↑15	↑47		↑94
Nmol/g liver		↑13	↑52	↑38	↑29	↓8	↑41	↑88		↑215
Nmol/total liver		↑11	↑110	↑86	↑129	↓8	↑31	↑89		↑403
Enzyme Induction										
% Δ from control										
PROD										
pmol/min/mg micros. protein		↓5	↑688	↑140	↑233	↑6	↑232	↑97		↑15
pmol/min/g liver		↑17	↑1053	↑210	↑287	no Δ	↑310	↑110		↑86
pmol/min/total liver		↑19	↑1568	↑332	↑615	↓1	↑275	↑107		↑198
EROD										
pmol/min/mg micros. protein		↓37	↓16	↓51	↓49	↓12	↑32	↑14		↑11
pmol/min/g liver		↓28	↑2	↓41	↓45	↓19	↑57	↑44		↑76
pmol/min/total liver		↓28	↑47	↓20	↓3	↓21	↑44	↑41		↑176

Shaded areas indicate a significant difference from vehicle controls.

Urinalysis: Urine volumes were increased in loratadine-treated animals and in males administered the mid-doses after 3 months treatment (Table 7). In addition, urine osmolarity was reduced in the same groups. Results in the high-dose DCL group were not consistent and may be due to the earlier sampling time for this group.

Table 7. Urinalysis results in rats following 3-month administration.

Urinalysis	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	3	30	60	120*	120-L	3	30	60	120*	120-L
4-hour volume										
% Δ from control	28	35	11	-39	44	-10	20	66	3	39
24-hour volume										
% Δ from control	13	87	53	-19	62	-2	21	20	20	99
Osmolarity										
% Δ from control	-17	-51	-43	6	-55	8	-17	-56	-18	-43

Shaded areas indicate statistically significant difference from control group (p < 0.05).

120-L: 120 mg/kg loratadine active control group.

* Day 22/23.

Organ Weight: The high-dose female desloratadine group was not assessed due to high mortality and only one high-dose male was assessed. Findings from the other dose groups demonstrated increases in liver, lung, adrenal, heart and kidney weights, and decreases in spleen, thymus and

uterus weights (Table 8). The active control group was generally comparable to the mid-dose groups.

Table 8. Organ weight changes in rats following 3-month administration.

Organ weight	Males					Females				
	3	30	60	120	120-L	3	30	60	120	120-L
Dose group (mg/kg) n =	3	30	60	120	120-L	3	30	60	120	120-L
	10	10	10	1	10	10	8	4	0	4
Liver										
AOW-% Δ from control	3	27	48	10	69	4	4	10		76
RTB	4	34	78	127	101	5	16	44		121
RTBr	6	31	53	15	73	1	5	15		87
Lungs										
AOW-% Δ from control	-11	20	44	40	22	10	68	130		105
RTB	-10	27	73	187	46	11	88	197		156
RTBr	-9	24	49	46	25	7	70	138		119
Spleen										
AOW-% Δ from control	-2	-24	-24	-52	-17	-4	-18	-30		-15
RTB	-1	-19	-8	-2	-1	-3	-9	-10		7
RTBr	1	-21	-21	-50	-15	-7	-17	-27		-10
Thymus										
AOW-% Δ from control	11	-4	-23	-43	-3	19	-11	-31		-36
RTB	10	3	-7	18	15	20	no Δ	-11		-20
RTBr	14	-1	-20	-40	-1	15	-11	-28		-32
Uterus										
AOW-% Δ from control						32	22	-47		-51
RTB						33	35	-33		-38
RTBr						28	24	-45		-48
Adrenals										
AOW-% Δ from control	-3	-10	-11	41	-4	2	-6	11		13
RTB	-3	-6	7	188	14	2	5	45		44
RTBr	1	-7	-7	48	-1	-2	-5	15		20
Brain										
AOW-% Δ from control	-3	-3	-4	-4	-3	3	-1	-4		-6
RTB	-3	3	15	96	16	4	11	25		19
Heart										
AOW-% Δ from control	-3	-7	-11	-18	-9	4	-4	-7		-1
RTB	-3	-2	7	67	7	5	8	22		25
RTBr	no Δ	-4	-8	-15	-7	1	-3	-3		6
Kidneys										
AOW-% Δ from control	1	-4	-3	33	-1	2	1	22		48
RTB	1	2	16	173	18	3	13	59		90
RTBr	4	no Δ	no Δ	38	2	-1	3	27		57

Shaded areas indicate statistically significant difference from control group ($p < 0.05$).

120-L: 120 mg/kg loratadine (active control group).

AOW: Absolute organ weight RTB: Relative to body weight RTBr: Relative to brain weight

Gross Pathology: The primary gross findings following the final sacrifice were likely due to the pharmacological effects of the drug and included dilatation in the gastrointestinal tract, the kidney, uterus and urinary bladder at a slightly higher incidence in drug-treated animals than in

controls (Table 9). Kidney discoloration and heart foci were also noted. In animals dying early, these findings, as well as stomach discoloration and reduced spleen and thymus size, were reported.

Table 9. Gross observations in rats following 3-month oral administration.

Observation	Males						Females					
Final sacrifice												
Dose (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
n =	10	10	10	10	1	10	10	10	8	4	0	4
Colon - dilatation	0	0	0	0	0	1	0	0	0	0	0	0
Heart - focus	0	0	0	0	0	1	0	0	0	0	0	0
Lg Intest. - dilatation	0	0	0	0	1	0	0	0	0	0	0	0
Kidney – discoloration	0	0	0	0	1	1	0	0	0	1	0	1
- dilatation	1	0	0	2	0	1	0	0	0	0	0	1
Testis - small	1	0	0	1	0	4						
Urinary bladder - dilatation	0	0	0	0	0	1	0	0	0	0	0	0
Uterus – dilatation							0	2	1	0	0	0
-small							0	0	0	1	0	1
Unscheduled deaths												
n =	0	0	0	0	9	0	0	0	2	6	10	6
Cecum - dilatation	0	0	0	0	1	0	0	0	0	1	0	3
Colon – dilatation	0	0	0	0	0	0	0	0	0	1	1	4
- dilated/impacted	0	0	0	0	0	0	0	0	0	0	1	0
Duodenum - dilatation	0	0	0	0	0	0	0	0	0	1	0	0
Ileum - dilatation	0	0	0	0	1	0	0	0	0	1	0	0
Lg Intest. – dilatation	0	0	0	0	1	0	0	0	0	0	2	0
- impaction	0	0	0	0	0	0	0	0	0	0	3	0
- stricture	0	0	0	0	0	0	0	0	0	0	1	0
Jejunum – dilatation	0	0	0	0	1	0	0	0	0	1	0	0
Kidney – discoloration	0	0	0	0	1	0	0	0	0	0	0	0
- dilatation	0	0	0	0	0	0	0	0	0	0	0	1
Liver – discoloration	0	0	0	0	0	0	0	0	0	0	1	0
- focus	0	0	0	0	0	0	0	0	0	0	0	1
Spleen – focus	0	0	0	0	1	0	0	0	0	0	0	0
-small	0	0	0	0	3	0	0	0	0	0	5	1
Stomach – dilatation	0	0	0	0	0	0	0	0	0	1	1	0
-discoloration	0	0	0	0	1	0	0	0	0	0	0	0
-enlarged	0	0	0	0	1	0	0	0	0	0	0	0
Thymus - small	0	0	0	0	0	0	0	0	0	0	1	0
Uterus - dilatation	0	0	0	0	0	0	0	0	1	0	0	0

Histopathology: Histological findings are summarized in Table 10. The primary findings were ubiquitous indicators of systemic phospholipidosis and included vacuolation, atrophy, necrosis, fibrosis and inflammatory cell infiltration. Findings were generally of greatest incidence and severity at the high SCH 34117 dose, while findings at the dose of 60 mg/kg was comparable to those at 120 mg/kg loratadine.

Table 10. Histological changes in rats following 3-month administration.

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Adrenals – vacuolation	10	0	0	10	10	10	10	0	0	10	10	10
Minimal	0			0	7	0	0			2	1	4
Mild	0			0	0	0	0			0	9	2
Brain – vacuolation of choroid plexus	10	0	0	10	10	10	10	0	0	10	10	10
Minimal	0			0	2	0	0			2	2	5
Mild	0			0	8	0	0			6	5	1
Moderate	0			0	0	0	0			1	3	3
Bone – cell infiltr, mononuc cell, myofiber	10	0	10	10	10	10	10	0	10	10	10	10
Minimal	0		0	0	5	0	0		0	6	1	5
Mild	0		0	0	5	0	0		0	1	7	4
Moderate	0		0	0	0	0	0		0	0	2	0
Vacuolation – myofiber												
Minimal	0		0	0	6	0	0		0	7	0	6
Mild	0		0	0	3	0	0		0	2	10	3
Moderate	0		0	0	1	0	0		0	0	0	0
Fibrosis, myofiber												
Minimal	0		0	0	6	0	0		0	2	2	5
Mild	0		0	0	0	0	0		0	2	7	4
Degeneration, myofiber												
Minimal	0		0	0	9	0	0		0	5	6	8
Mild	0		0	0	0	0	0		0	2	0	0
Moderate	0		0	0	0	0	0		0	1	0	0
Bone marrow –	10	0	10	10	10	10	10	0	10	10	10	10
Hypercellularity – min	0		0	0	0	2	0		0	2	0	0
Hypocellularity – min	0		0	0	1	0	0		0	0	4	2
- mild	0		0	0	2	0	0		0	0	0	1
Mastocytosis – min	0		0	0	1	0	0		0	0	0	0
- mild	0		0	0	1	0	0		0	0	0	0
Vacuolation – scattered												
minimal	0		0	0	5	0	0		0	2	2	5
mild	0		0	0	3	0	0		0	1	5	1
moderate	0		0	0	1	0	0		0	0	3	1
Atrophy, fat												
Mild	0		0	0	1	0	0		0	0	0	0
Moderate	0		0	0	6	0	0		0	0	8	3
Epididymides	10	10	10	10	10	10						
Cellular debris, luminal												
Minimal	1	0	2	3	7	0						
Mild	0	0	3	6	2	8						
Moderate	0	0	0	0	0	1						
Vacuolation, epithel												
Minimal	1	0	6	1	0	2						
Mild	0	0	0	4	2	4						
Moderate	0	0	0	5	8	4						
Oligospermia												
Minimal	0	0	0	0	2	0						

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Mild	0	0	1	0	1	2						
Moderate	1	0	0	1	0	2						
Severe	0	0	0	0	0	1						
Eyes – vacuolation of	10	0	10									
Ciliary body, m-phage												
Minimal	0		0	0	6	0	0	0	0	1	8	0
Vacuolation, myofiber												
Minimal	0		0	6	5	5	0		1	10	7	10
Mild	0		0	0	5	0	0		0	0	3	0
Vacuolation, retinal, epithelium												
minimal	0		0	0	5	0	0	0	0	5	5	3
Gliosis – minimal	0		0	0	1	0	0	0	0	0	0	0
Heart	10	0	10									
Cell. Infiltration mononuclear cell												
Minimal	0		0	0	5	2	0	0	0	1	4	7
Mild	0		0	0	1	0	0	0	0	1	3	2
Vacuolation, myofiber, base												
Minimal	0		0	1	6	4	2	2	6	6	3	3
Mild	0		0	0	0	0	0	0	0	2	0	6
Vacuolation, myofiber, Interstitial												
Minimal	0		0	0	8	0	0	0	0	3	2	1
Mild	0		0	0	0	0	0	0	0	0	8	5
Degeneration, myofiber minimal	1		0	0	3	0	1	1	1	0	0	0
Kidneys	10	0	10									
Vacuolation, epithel												
Minimal	0		0	9	1	7	0	0	3	3	3	0
Mild	0		0	1	4	2	0	0	0	4	5	5
Moderate	0		0	0	5	0	0	0	0	3	2	5
Necrosis												
Minimal	2		0	6	9	5	0	0	1	6	6	7
Hyperplasia, epith, pelv												
Mild	0		0	0	0	1	0	0	0	0	0	0
Erosion, pelvis												
Moderate	0		0	0	0	1	0	0	0	0	0	0
Dilatation, tubular												
Minimal	1		0	0	2	1	0	0	0	1	2	0
Mild	0		0	0	0	0	0	0	0	1	0	2
Moderate	0		0	0	1	0	0	0	0	0	0	0
Lymph nodes	10	1	10	10	10	10						
Vacuolation, m-phage												
Minimal	0	0	1	5	0	2	0	0	0	3	0	1
Mild	0	0	0	0	4	0	0	0	0	7	3	6

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Moderate Atrophy, lymphoid	0	0	0	0	6	0	0	0	0	0	7	3
Minimal	0	0	0	0	3	0	0	0	0	2	2	3
Mild	0	0	0	0	0	0	0	0	0	1	5	2
Moderate	0	0	0	0	6	0	0	0	0	0	3	2
Liver	10											
Cell. Infiltr., mononuc. cell, decreased	0	0	0	1	10	2	0	0	0	4	8	7
Vacuolation, kupfer cell												
Minimal	0	0	0	0	4	0	0	0	0	1	4	8
Mild	0	0	0	0	5	0	0	0	0	0	5	1
Moderate	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, centrilob. hepatocellular												
Minimal	0	0	0	5	1	1	0	0	0	8	1	4
Mild	0	0	0	1	7	1	0	0	0	1	9	6
Moderate	0	0	0	0	2	0	0	0	0	0	0	0
Vacuolation, biliary, epithelium												
Minimal	0	0	0	6	0	4	0	0	2	1	0	0
Mild	0	0	0	1	1	2	0	0	1	2	0	2
Moderate	0	0	0	0	6	0	0	0	0	4	1	5
Severe	0	0	0	0	3	0	0	0	0	3	9	3
Hypertrophy, centrilob												
Minimal	0	0	0	0	1	0	0	0	5	5	1	2
Mild	0	0	4	2	8	0	0	0	3	2	9	4
Moderate	0	0	6	8	0	10	0	0	0	1	0	4
Lungs	10	0	10									
Vacuolation, epithel	0		0	7	6	3	0	0	4	4	2	6
Minimal	0		0	0	2	1	0	0	0	3	8	4
Mild												
Vacuolation, alv mac	0		0	1	1	4	0	0	5	0	8	3
Minimal	0		0	9	8	4	0	0	2	6	2	5
Mild	0		0	0	1	0	0	0	0	4	0	2
Moderate												
Material, proteinacious, alveolar	0		0	3	6	0	0	0	0	4	9	1
Minimal	0		0	0	3	0	0	0	0	1	1	0
Mild	0		0	0	1	0	0	0	0	3	0	9
Moderate												
Esophagus	10	0	10									
Cell infiltr, mononuc cell												
minimal	0		0	0	6	1	0	0	0	5	5	6
mild	0		0	0	0	0	0	0	0	0	0	1
Vacuolation, myofiber												

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
minimal	0	0	3	2	1		0	0	1	3	1	0
mild	0	0	0	5	0		0	0	0	6	9	10
Degeneration, myofiber												
minimal	0	0	1	2	0		0	0	1	1	1	2
Ovaries							10	10	10	10	10	10
Vacuolation, sex cord												
Minimal							0	0	0	9	10	10
Mild							0	0	0	1	0	0
Vacuolation, corp lutea												
Minimal							0	0	0	1	2	0
Mild							0	0	0	4	7	4
Moderate							0	0	0	4	1	5
Severe							0	0	0	0	0	1
Vacuolation, rete ducts												
Minimal							0	0	0	2	0	0
Mild							0	0	1	0	1	1
Moderate							0	0	0	0	2	1
Severe							0	0	0	0	1	0
Necrosis, granulosa cell												
Minimal							0	0	0	0	6	3
Mild							0	0	0	0	1	1
Atrophy, follicular												
Minimal							0	0	0	0	1	1
Pancreas	10	10	10	10	10	10	10	10	10	10	10	10
Single cell necrosis												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, ductular												
Minimal	0	0	0	6	0	0	0	0	1	1	0	0
Mild	0	0	0	0	2	0	0	0	0	3	1	6
Moderate	0	0	0	0	6	0	0	0	0	0	4	2
Severe	0	0	0	0	2	0	0	0	0	1	5	1
Vacuolation, acinar cell												
Minimal	1	1	2	0	0	2	0	0	0	1	4	2
Mild	0	0	0	0	8	0	0	0	0	2	3	3
Moderate	0	0	0	0	0	0	0	0	0	0	2	0
Parathyroid glands	5	0	0	7	9	8	7	0	9	7	7	9
Vacuolation, chief cell												
Minimal	0			0	9	0	0		0	4	7	8
Mild	0			0	0	0	0		0	2	0	1
Pituitary gland	10	0	10	10	10	10	10	0	10	10	10	10
Vacuolation, pars anterior												
Minimal	0	0	1	9	2		0	0	10	10	10	
Prostate	10	0	10	10	10	10						
Vacuolation, epithel												
Minimal	0	0	1	2	0							
Mild	0	0	0	6	1							

Histopathology	Males					Females						
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Moderate Immaturity	0		0	0	1	0						
Minimal Immaturity	0		0	0	7	0						
Salivary gland	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, sublingual, ductular												
Minimal	0			0	1	0	0	0	1	0	0	0
Mild	0			0	1	0	0	0	0	3	0	0
Moderate	0			0	7	0	0	0	8	7	10	0
Severe	0			0	1	0	0	0	0	0	0	0
Vacuolation, sublingual, acinar cell												
Minimal	0			0	5	0	0	0	8	7	8	0
Mild	0			0	4	0	0	0	0	3	2	0
Vacuolation, parotid, ductular												
Minimal	0			0	5	0	0	0	4	6	5	0
Mild	0			0	3	0	0	0	2	4	5	0
Moderate	0			0	2	0	0	0	1	0	0	0
Vacuolation, parotid, acinar cell												
Minimal	9			7	0	3	6	8	4	0	1	0
Mild	0			0	4	0	0	0	2	6	7	0
Moderate	0			0	5	0	0	0	0	4	0	0
Vacuolation, submandib, ductular												
Minimal	0			0	2	0	0	0	4	0	2	0
Mild	0			0	4	0	0	0	5	6	5	0
Moderate	0			0	3	0	0	0	0	4	3	0
Severe	0			0	1	0	0	0	0	0	0	0
Vacuolation, submandib, acinar cell												
Minimal	0			0	3	0	0	0	5	3	1	0
Mild	0			0	0	0	0	0	0	1	0	0
Moderate	0			0	0	0	0	0	0	3	0	0
Necrosis, parotid												
Minimal	0			0	2	0	0	1	1	0	0	0
Necrosis, submandib												
Minimal	0			0	2	0	0	0	0	2	0	0
Atrophy, sublingual												
Minimal	0			0	8	0	0	0	5	4	8	0
Mild	0			0	0	0	0	0	0	6	2	0
Atrophy, parotid												
Minimal	0			0	3	0	0	0	0	1	2	0
Mild	0			0	3	0	0	0	0	3	0	0
Moderate	0			0	2	0	0	0	1	2	1	0
Severe	0			0	2	0	0	0	0	4	2	0
Atrophy, submandib												
Minimal	0			0	4	0	0	0	7	2	2	0

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Vacuolation, epithel												
Minimal	0			0	4	0	0	0	0	1	4	2
Mild	0			0	0	0	0	0	0	0	0	1
Pigment accum, lumina												
Minimal	0			0	6	0	0	0	0	0	1	2
Atrophy												
Minimal	1			0	5	0	0	0	1	3	5	7
Mild	0			0	0	0	0	0	0	0	1	0
Stomach	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, epith												
Minimal	0			0	4	0	0		0	0	2	0
Vacuolation, myofiber												
Minimal	0			0	2	0	0		0	2	1	2
Mild	0			0	7	0	0		0	4	9	5
Necrosis, mucosal												
Minimal	0			0	1	0	0		0	0	0	0
Congestion, mucosal												
Minimal	0			0	1	0	0		0	0	0	0
Large intestine	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, lymphoid nodule, macrophage												
Minimal	0			0	1	0	0		0	0	1	0
Mild	0			0	1	0	0		0	0	0	0
Vacuolation, myofiber												
Minimal	0			0	8	0	0		0	0	3	0
Mild	0			0	0	0	0		0	2	5	2
Dilatation, luminal												
Minimal	0			0	0	0	0		0	0	0	0
Mild	0			0	1	0	0		0	0	0	0
Severe	0			0	0	0	0		0	0	1	3
Small intestine	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, lymphoid nodule, macrophage												
Minimal	0			0	3	0	0		0	1	0	0
Vacuolation, duodenal gland												
Minimal	0			0	7	0	0		0	5	7	5
Vacuolation, lamina propria, macrophage												
Minimal	0			0	6	0	0		0	2	5	3
Mild	0			0	6	0	0		0	0	5	0
Severe	0			0	3	0	0		0	3	6	4
Vacuolation,												
Minimal	0			0	0	0	0		0	1	1	0

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Atrophy, lymphoid												
Minimal	0	0	0	0	1	0	0	0	0	1	1	0
Moderate	0	0	0	0	1	0	0	0	0	1	4	3
Severe	0	0	0	0	5	0	0	0	0	0	5	1
Tongue	10	0	0	10	10	10	10	0	10	10	10	10
Cell. infiltr., mononuc cell,												
Minimal	0		0	8	0	0	0	1	5	2		
Mild	0		0	1	0	0	0	0	3	0		
Moderate	0		0	0	0	0	0	0	1	0		
Vacuolation												
Minimal	0		0	9	0	0	0	7	1	8		
Mild	0		0	1	0	0	0	2	9	1		
Fibrosis, interstitial												
Minimal	0		0	0	0	0	0	0	3	0		
Trachea	10	0	10	10	10	10	10	10	10	10	10	10
Vacuolation, m-phage												
Minimal	0		0	1	0	0	0	0	0	2	3	
Mild	0		0	0	0	0	0	0	2	6	0	
Moderate	0		0	0	0	0	0	0	0	0	1	
Vacuolation, epithel												
Minimal	0		0	3	1	5	0	0	3	0	0	0
Mild	0		0	5	5	0	0	0	0	3	7	9
Moderate	0		0	4	0	0	0	0	4	3	1	
Necrosis, epithelial												
Severe	0		0	0	0	0	0	0	1	1	0	
Uterus							10	10	10	10	10	10
Immaturity												
Minimal							0	0	0	2	1	0
Mild							0	0	0	1	2	0
Moderate							0	0	0	1	3	8
Severe							0	0	0	0	3	0
Vacuolation, myometr												
Minimal							0	0	0	4	5	1
Mild							0	0	0	1	5	5
Vacuolation, endometrium, m-phage												
Minimal							0	0	2	4	1	2
Mild							0	0	0	5	8	6
Moderate							0	0	0	0	1	1
Vacuolation, epithel												
Minimal							0	0	2	5	0	1
Mild							0	0	0	3	1	3
Moderate							0	0	0	2	9	6
Urinary bladder	10	0	0	10	10	10	10	10	10	10	10	10
Vacuolation, epithel												
Minimal	0		0	3	2	0	0	0	2	1	2	
Mild	0		0	5	0	0	0	0	2	6	3	
Moderate	0		0	2	0	0	0	0	1	2	3	
Vacuolation, myofiber												

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Minimal	0			0	6	0	0	0	2	4	5	4
Mild	0			0	4	0	0	0	0	0	4	1
Vagina							10	0	10	10	10	10
Cell infiltr, mononuc cell, myofiber							0		0	1	2	4
Minimal												
Vacuolation, m-phage							0		0	3	0	0
Minimal							0		0	1	7	6
Mild							0		0	0	3	2
Moderate												
Vacuolation, myofiber							0		0	3	3	5
Minimal							0		0	2	5	5
Mild												
Vacuolation, urethral							0		0	0	1	0
Minimal												
Vacuolation, epithel							0		0	1	6	3
Minimal							0		0	1	3	5
Mild												
Mammary glands	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation												
Minimal	0			0	0	0	0		0	5	1	4
Mild	0			0	0	0	0		0	4	9	5
Atrophy												
Minimal	0			0	2	0	0		0	0	0	0
Mild	0			0	2	0	0		0	0	0	0
moderate	0			0	2	0	0		0	0	0	0

120-L: 120 mg/kg loratadine active control group.

Toxicokinetics: Plasma concentrations increased supra-proportionally in a dose-dependent manner and were gender-dependent with exposure greater by up to 3.3-fold in females than in

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males following administration of SCH 34117 and loratadine (Table 11). SCH 34117 was slowly absorbed. The SCH 34117 exposure resulting from loratadine administration was similar to that observed at 60 mg/kg SCH 34117. Drug accumulation was observed with multiple dose administration, especially at the lowest dose. Loratadine exposure following loratadine administration was approximately 7 to 10-fold less than corresponding SCH 34117 exposure indicating extensive metabolism of loratadine.

Table 11. Toxicokinetics of SCH 34117 and loratadine.

Parameter		Dose (mg SCH 34117/kg)								Dose (mg SCH 29851/kg)	
		3		30		60		120		120	
		Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9
SCH 34117											
Cmax (ng/ml)	Males	23.7	252	611	1150	1590	1650	2010	*	1250	2990
	Females	77	200	1000	2140	2140	4770	2320	*	1950	3370
Tmax (hr)	Males	2.5	8	4	12	8	12	12	*	2.5	4
	Females	1	2.5	8	12	8	2.5	4	*	8	12
AUC (0-24 hr) (ng.hr/ml)	Males	169	1950	9490	26100	29000	34500	39000	*	23900	37800
	Females	556	1890	17700	42600	39800	69200	46300	*	39000	64200
R	Males		11.5		2.8		1.2		*		1.6
	Females		3.4		2.4		1.7		*		1.6
SCH 29851											
Cmax (ng/ml)	Males									858	560
	Females									1260	779
Tmax (hr)	Males									1	2.5
	Females									1	1
AUC (0-24 hr) (ng.hr/ml)	Males									4070	3940
	Females									5480	5990
R	Males										--
	Females										1.09

R = AUC (0-24 hr) week 9 / AUC (0-24 hr) day 1

NA: not applicable

* not assessed due to high mortality

A NOAEL of 3 mg/kg and 30 mg/kg was identified in females and males, respectively, due to kidney necrosis and reduced body weight gain. Systemic phospholipidosis (primarily vacuolation, atrophy and necrosis) was the main toxicity and was noted in organ systems throughout the body. Toxicity was more prominent in SCH 34117-treated animals based on a mg/kg basis. However, the toxicity profile was similar between the loratadine-treated group and the 60 mg/kg SCH 34117 as indicated by the pharmacokinetic similarities between the two groups.

Monkey, 3-Month Oral (Gavage) Toxicity

Study #: N003134G Schering Study #: 98212 Report #: P-6976 Volume: 23.4

Study Dates: Starting date: 7/1/1998; report issued: 6/1999
Testing Lab: XXXXXXXXXX
Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not provided); SCH 29851 (Batch MI-A-00851; purity not provided)
Concentration: 1.2 to 14.4 mg/ml
Dose Volume: 5 ml/kg
GLP: This report was submitted with a signed GLP statement.
QA report: Yes.

Methods: Cynomolgus monkeys were assigned to the following treatment groups:

Dose	0	6	12	18/24*	22/72*
(mg SCH 34117/kg/day):	mg loratadine/kg/day				
No./sex	4	4	4	4	4

*: Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months. The following observations were made:

Clinical observation . . . daily
 Body weight weekly
 Food consumption . . . daily
 Water consumption . . . not assessed
 Exam twice pre-study, Days 28 and 79; included body temperature, heart rate, and respiration rate
 Ophthalmoscopy Pre-test and week 12
 ECG Days -2, -5, 28 and 79; assessment included body temperature, heart rate, respiration, systolic blood pressure, diastolic blood pressure
 Hematology Days -12 and -5, and Days 23 and 92
 Clinical chemistry Weeks -2, and Days 12 and 24
 Urinalysis Days -12/13 and -5/6, and Days 22/23 and 91/92
 Enzyme induction Liver samples assayed for protein content, cytochrome P450 content, and 7-ethoxyresorufin O-deethylase. Results to be reported separately by sponsor.
 Organ weights at sacrifice (for specific tissues/organs see Addendum, page 32)
 Gross pathology at sacrifice
 Histopathology at sacrifice; organs/tissues collected from the control (vehicle and active), high-dose monkeys, monkeys sacrificed moribund and all gross lesions (for specific tissues/organs see Addendum, page 32).

Toxicokinetics samples taken from 2 animals/sex/group/time point at 1, 2, 4, 8, 12 and 24 hours after dosing on Days 1 and during week 9.

Results:

Mortality: One female treated with loratadine died on day 57. The sponsor did not provide a cause of death.

Clinical Observations: Anti-cholinergic effects, mainly in the high-dose group, were the primary drug-related clinical observations in this study (Table 11). These included few or no feces at the mid- and high-dose of SCH 34117 and loratadine-treated animals. A slight increase in the incidence of extended abdomen and hunched posture were also noted in these groups. Emesis (non-severe) occurred in only a few animals and on only 1-2 occasions per animal. Other findings unique to the loratadine-treated animals were also reported.

Table 11. Clinical observations in monkeys following 3-month administration of SCH 34117.

Observation	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - loratadine	0	6	12	18/24	22/72 - loratadine
Abrasion - foot	0	0	0	0	1	0	0	0	0	0
- head	0	0	0	0	1	0	0	0	0	0
Alopecia - leg	0	0	0	0	2	0	0	1	0	0
Emesis	0	0	1	2	0	1	0	1	1	0
Feces - few	0	0	0	4	1	0	0	0	2	3
Feces - none	0	0	0	4	2	0	0	1	3	2
Feces - mucoid	0	0	0	0	0	0	0	0	0	1
Discoloration - body	0	0	0	1	0	0	0	0	0	0
Extended abdomen	0	0	0	1	1	0	0	0	0	2
Hunched posture	0	0	0	1	1	0	0	0	0	1
Lethargic	0	0	0	0	1	0	0	0	0	1
Swelling - foot	0	0	0	0	0	0	0	0	1	0
- leg	0	0	0	0	0	0	0	0	1	0

Few feces: first observed days 71-80 (F) and 66-71(M). F: lasted for 1 d at HD 34117, 11 d at 22 L. M: 14 d at HD 34117, 26 d at 22 L.

No feces: first observed days 72-83 (F) and 78-84 (M). F: lasted for 1 d at MD 34117, 5 d at HD 34117, and 1 d at 22 L. M: 3 d at HD 34117, 8 d at 22 L.

Body Weight: A dose-dependent decrease in body weight gain was noted in males following 3 months treatment with 6, 12 or 18/24 mg/kg SCH 34117 (Table 12). In females, however, body weight gain was increased in SCH 34117-treated animals. High data variability was present. Loratadine-treated animals demonstrated a 33-53% decrease in body weight gain.

Table 12: Alterations in body weight gain at Day 92.

Dose (mg/kg)	Males				Females			
	6	12	18/24	22/72-L	6	12	18/24	22/72-L
Body weight gain								
% Δ from control	↓44	↓58	↓93	↓53	↑250	↑167	↑150	↓33

Food consumption: No consistent changes in food consumption were noted in treated animals compared to control animals.

Ophthalmoscopy: No treatment-related effects were noted.

Health Exam: No drug-related effects on body temperature, heart rate or respiration were reported following 3-month drug administration.

ECG: All ECGs were within normal limits and no changes appeared to be drug related. QT and QTc intervals were not significantly affected by drug treatment.

Hematology: No treatment-related effects were noted following the three month administration.

Clinical Chemistry: In males treated with SCH 34117, reduced levels of cholesterol, AP and GGT and increased levels of AST and ALT were noted primarily at the high dose (Table 13). Loratadine-treated males showed similar effects to the high dose males. Increased levels of AST and decreased levels of AP were also noted in high-dose females. These findings, in addition to decreased cholesterol, were also noted in the loratadine-treated females.

Table 13: Clinical chemistry findings following 3-month drug administration.

Clinical chemistry	Males				Females			
	Dose group (mg/kg)				Dose group (mg/kg)			
	6	12	18/24*	22/72-L	6	12	18/24*	22/72-L
Alkaline phosphatase % Δ from control	↓15	↓25	↓61	↓53	↑16	↑9	↓24	↓14
Aspartate aminotransferase % Δ from control	↑6	↑12	↑47	↑47	↑15	↑30	↑52	↑78
Alanine aminotransferase % Δ from control	↓13	↑22	↑50	↑102	↓23	↓9	↑4	↑81
Gamma glutamyl transferase % Δ from control	↓18	↓23	↓47	↓46	↑9	↑7	↓12	↑1
Cholesterol % Δ from control	↑15	↑3	↓22	↓25	--	↑1	↑9	↓21

* Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Urinalysis: No significant treatment-related effects were noted although a large degree of variability was apparent in the data set.

Organ Weight: No statistically significant changes in absolute organ weight or organ weight changes relative to body or brain weight were observed. However, mean absolute organ weight values did suggest slight to moderate reductions in heart, spleen, testes, prostate, epididymes, and thymus in males and the uterus, ovaries and thymus in females (Table 14). Data variability was high. In addition, increased liver weight was noted in loratadine-treated animals.

Table 14: Organ weight changes following 92-day drug administration

Absolute organ weight	Males				Females			
	Dose group (mg/kg)				Dose group (mg/kg)			
	6	12	18/24*	22/72-L	6	12	18/24*	22/72-L
Liver								
% Δ from control	↓7	↓1	↑8	↑20	↓7	↓4	↑12	↑35
Heart								
% Δ from control	↓13	↓13	↓25	↓5	↓3	↑8	↑12	--
Spleen								
% Δ from control	↓23	↓16	↓36	↓27	↓19	↓16	↑1	↓7
Testes								
% Δ from control	↓24	↓52	↓62	↓78				
Prostate								
% Δ from control	↓30	↓48	↓51	↓58				
Epididymes								
% Δ from control	↓29	↓38	↓55	↓59				
Thymus								
% Δ from control	↓21	↓11	↓64	↓52	↓19	↓17	↓37	↓40
Uterus								
% Δ from control					↑11	↓8	↓17	↓40
Ovaries								
% Δ from control					↑7	↓21	↓31	↓21

*: Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Gross Pathology: The primary gross findings included dilatation of the cecum and colon which are likely related to the decreased fecal excretion noted above (Table 15). Findings of splenic adhesion and deformity in a high dose male and dilatation of other organs of the digestive system in 1 loratadine-treated female were also observed.

Table 15. Gross observations in monkeys (4/group) following 3-month oral administration.

Gross observations	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - L	0	6	12	18/24	22/72 - L
Cecum - dilatation	0	0	0	2	2	0	1	0	1	2
Colon - dilatation	0	0	0	2	2	0	1	0	1	2
Duodenum - dilatation	0	0	0	0	0	0	0	0	0	1
Ileum - dilatation	0	0	0	0	0	0	0	0	0	1
Jejunum - dilatation	0	0	0	0	0	0	0	0	0	1
Stomach - dilatation	0	0	0	0	0	0	0	0	0	1
Heart - focus	0	0	0	0	0	0	0	0	1	0
Spleen - adhesion	0	0	0	1	0	0	0	0	0	0
- deformity	0	0	0	1	0	0	0	0	0	0

Histopathology: The primary microscopic findings in this study were indicative of systemic phospholipidosis such as vacuolation which occurred in multiple organs (Table 16). Other findings included atrophy, cellular infiltration and pigment accumulation. Findings at the high dose of SCH 34117 were comparable to those observed following administration of loratadine. In addition, ovarian mineralization was noted in high dose-SCH 34117 females and loratadine treated females. This finding was not addressed by the sponsor and was also noted in the 14-day and 6-week monkey studies.

Table 16: Histological findings following 3-month drug administration.

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Adrenals n =	4	0	0	4	4	4	0	0	4	4
Eosinophilia										
Minimal	1			0	1	1			0	0
Mild	0			1	0	0			1	0
Moderate	0			0	1	0			0	1
Vacuolation, cortex, MF										
Mild	0			1	0	0			0	0
Brain	4	0	0	4	4	4	0	0	4	4
Corpora amylacea - Minimal	2			4	4	2			2	4
Bone	4	4	4	4	4	4	4	4	4	4
Vacuolation – myofiber										
Minimal	0	0	0	1	1	0	0	0	0	1
Mild	0	0	0	0	0	0	0	0	0	1
Bone marrow	4	4	4	4	4	4	4	4	4	4
Vacuolation – macrophage										
minimal	0	0	0	1	1	0	0	0	1	1
Atrophy, fat										
Mild	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	1
Eyes	4	0	0	4	4	4	0	0	4	4
Cellular infiltration, mononuc cell										
Minimal	0			1	0	0			1	0
Metaplasia, focal, corneal										
Minimal	0			1	0	0			0	0
Kidneys	4	0	0	4	4	4	0	0	4	4
Tubular basophilia - Minimal	0			0	0	0			1	0
Mineralization - Minimal	1			2	2	1			0	1
Fibrosis - Minimal	0			0	1	0			0	0
Cast(s) – minimal	0			1	0	0			1	0
Atrophy, tubular - minimal	0			0	1	0			1	0
Lymph nodes	4	4	4	4	4	4	0	0	4	4
Cellular infiltration, leukocyte										
Minimal	0	0	0	0	0	0			1	0
Apoptosis – minimal	0	0	0	0	0	0			1	0
Vacuolation – minimal	0	0	0	1	2	0			0	1
Hematopoiesis, extramedullary										
Minimal	0	0	0	0	0	0			1	0
Mild	0	0	0	1	0	0			0	3
Atrophy, lymphoid										
Minimal	0	0	0	0	1	1			0	0

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Mild	0	0	0	1	0	0			0	1
Moderate	0	0	0	1	0	0			0	0
Liver	4	4	4	4	4	4	4	4	4	4
Vacuolation, sinusoidal										
Minimal	0	0	0	0	1	0	0	0	0	0
Vacuolation, hepatocell, scattered										
Minimal	0	0	0	1	2	1	0	0	1	0
Vacuolation, hepatocell, periportal										
Mild	0	0	0	0	0	0	0	0	0	1
Vacuolation, biliary, epithelium										
Mild	0	0	0	1	1	0	0	0	1	1
Pigment accumulation										
Minimal	0	0	0	1	0	0	0	0	0	0
Fibrosis, capsular										
Minimal	0	0	0	1	0	0	0	0	0	0
Lungs	4	4	4	4	4	4	4	4	4	4
Vacuolation, alveolar macrophage										
Minimal	0	0	0	2	2	1	0	0	3	1
Mild	0	0	0	2	1					
Vacuolation, bronchial, epithelium										
Minimal	0	0	1	2	1	0	0	1	3	2
Mild	0	0	0	1	1	0	0	0	0	2
moderate	0	0	0	1	0	0	0	0	0	0
Esophagus	4	0	0	4	4	4	0	0	4	4
Cellular infiltration, mononuc cell										
Minimal	1	0	0	2	1	1	0	0	1	1
Ovaries						4	0	0	4	4
Mineralization										
Minimal						1			0	2
Mild						0			3	1
Pancreas	4	4	4	4	4	4	4	4	4	4
Vacuolation, ductular										
Minimal	0	0	0	0	0	0	0	0	0	1
Mild	0	0	0	0	1	0	0	0	1	0
Vacuolation, acinar										
Minimal	0	0	0	0	1	0	0	0	0	1
Parathyroid glands	4	4	3	4	4	4	4	4	4	4
Cellular infiltration, mononuc cell										
Minimal	0	0	0	0	1	0	0	0	0	0
Pituitary gland	4	0	0	4	4	4	0	0	4	4
Cellular infiltration, mononuc cell										
Minimal	0	0	0	0	0	0	0	0	1	0
Vacuolation, scattered, coarse										
Minimal	0	0	0	1	0	1	0	0	0	2
Salivary glands	4	4	4	4	4	4	4	4	4	4
Vacuolation, ductular, submandib										
Minimal	0	0	0	1	3	0	0	2	0	2
Mild	0	0	0	2	0	0	0	0	2	1

Histopathology	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	0	6	12	18/24	22/72	0	6	12	18/24	22/72
Mild	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	0	1	1	0	0	0	1	2
Trachea	4	4	4	4	4	4	4	4	4	4
Vacuolation, epithelial										
Minimal	0	0	0	0	1	0	0	0	0	1
Mild	0	0	0	2	0	0	0	0	1	2
Mammary glands	4	0	0	4	4	4	0	0	4	4
Cell infiltration, mononuc cell										
Minimal	0	0	0	0	3	0	0	0	4	3
Pigment accumulation										
Minimal	0	0	0	3	0	0	0	0	0	1
Mild	2	0	0	0	1	1	0	0	0	0

Toxicokinetics: SCH 34117 plasma concentrations increased in a dose-dependent manner and were gender independent following SCH 34117 administration. SCH 34117 was slowly absorbed, accumulating in plasma following multiple SCH 34117 dose administration. From the low to mid- SCH 34117 dose, exposure increased proportionally, while at the high-dose the increase was supra-proportional at Day 1 and Week 9 (Table 16). At day 1, 22 mg/kg loratadine resulted in SCH 34117 levels which were similar to those observed following 6 mg/kg SCH 34117. At week 9, the high-dose of 24 mg/kg SCH 34117 resulted in slightly lower systemic exposure (17%) to SCH 34117 than that observed following 72 mg/kg loratadine. Loratadine plasma concentrations were also gender independent. Although the loratadine dose was increased 3.3-fold, the systemic exposure to loratadine was reduced by 33% during week 9 compared to Day 1. SCH 34117 exposure following loratadine administration were ~ 5-times and 87-times greater than exposure to loratadine on Day 1 and Week 9, respectively. Comparatively, a single administration of 18 mg/kg SCH 34117 produced an ~ 4-fold greater exposure to SCH 34117 than did an equimolar (22 mg/kg) dose of loratadine.

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Table 16. Toxicokinetics of SCH 34117 and loratadine.

Parameter	Dose (mg SCH 34117/kg)						Dose (mg SCH 29851/kg)	
	6		12		18	24	22	72
	Day 1	Wk 9	Day 1	Week 9	Day 1	Week 9	Day 1	Week 9
SCH 34117								
Cmax (ng/ml)	500	770	769	1424	1209	2696	311	2894
Tmax (hr)	2	4	4	4	8	8	4	12
AUC (0-24 hr) (ng.hr/ml)	4937	11623	9821	21613	21422	54346	5494	65379
R	NA	2.35	NA	2.20	NA	NA	NA	NA
SCH 29851								
Cmax (ng/ml)							348	104
Tmax (hr)							1	1
AUC (0-24 hr) (ng.hr/ml)							1121	753

R = AUC (0-24 hr) week 9 / AUC (0-24 hr) day 1

NA: not applicable

A NOAEL dose of 12 mg/kg SCH 34117 was identified due to the induction of phospholipidosis (vacuolation, atrophy, necrosis) in organ systems throughout the body. The toxicity profiles observed in the high-dose SCH 34117 and loratadine-treated groups were similar at comparable SCH 34117 exposure levels.

Summary of Toxicology Studies

Two 3-month oral gavage toxicity studies were performed with SCH 34117 in rats (3, 30, 60, and 120 mg/kg SCH 34117 and an active control of 120 mg/kg loratadine) and monkeys (6, 12, and 18/24 mg/kg SCH 34117 and an active control of 22/72 mg/kg loratadine) in order to support clinical studies and bridging to the chronic toxicology program performed for loratadine. In rats, high mortality was observed in rats administered 120 mg/kg SCH 34117. The primary histological findings were indicative of systemic phospholipidosis and included vacuolation, atrophy, necrosis, fibrosis and inflammatory cell infiltration. Findings were generally of greatest incidence and severity at the high SCH 34117 dose, while findings at the dose of 60 mg/kg were comparable to those at 120 mg/kg loratadine. In addition, ovarian mineralization was noted in high-dose females. Organ weight changes were noted at 60 mg/kg SCH 34117 and with the active control and included increases in liver, lung, adrenal, heart and kidney weights, and decreases in spleen, thymus and uterus weights. Body weight gain was significantly reduced at doses of 30 mg/kg or greater in females and 60 mg/kg or greater in males. Reduced eosinophils and lymphocytes (49-79%) were noted at the high-dose and aspartate aminotransferase was significantly increased (250-489%) at the HD SCH 34117. Loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. Plasma concentrations increased supra-proportionally and were greater in females. Drug accumulation was observed with multiple dose administration. The SCH 34117 exposure resulting from loratadine administration was similar to that observed at 60 mg/kg SCH 34117. NOAELs of 3 mg/kg and 30 mg/kg were identified for females and males, respectively. In monkeys, histopathological findings included indicators of systemic phospholipidosis (vacuolation, fibrosis, atrophy) in organ systems throughout the body. Primary gross findings included dilatation of the organs of the digestive

system. Anti-cholinergic effects were noted clinically and body weight gain was dose-dependently reduced in males (44-93%) but increased (non-dose-dependently) in females (150-250%). Overall, findings at the high-dose of SCH 34117 were comparable to those observed following loratadine administration and mean systemic exposure to SCH 34117 between the two groups was within 17%. In addition, drug accumulation was observed at the two lower SCH 34117 doses and gender difference were not observed. A NOAEL of 12 mg/kg was identified in this study.

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Addendum: Histopathology inventory for IND 55,364.

* Organ weight obtained

Study No.	P-6526	D18289	SN 98088	P-6973	P-6527	SN 98089	P-6976
Duration	14-day	14-day	28-day	3-month	14-day	28-day	3-month
Species	rat	rat	rat	Rat	monkey	monkey	monkey
Adrenals	X*		X*	X*	X*	X*	X*
Aorta	X		X	X	X	X	X
Bone marrow smear	X		X	X	X		X
Bone (femur)	X		X	X	X	X	X
Bone (rib)					X	X	
Bone (strenum)	X		X		X	X	
Brain:	X*		X*	X*	X*	X*	X*
Cecum	X		X		X	X	
Cervix			X				
Colon	X		X		X	X	
Duodenum	X		X	X	X	X	X
Epididymis	X*		X*	X*	X*	X	X*
Esophagus	X		X	X	X	X	X
Eye	X		X	X	X	X	X
Fallopian tube							
Fat							
Gall bladder					X	X	X
Gross lesions	X	X			X	X	X
Harderian gland	X		X	X			
Heart	X*		X*	X*	X*	X*	X*
Hypophysis							
Ileum	X		X	X	X	X	X
Injection site	NA	NA	NA		NA	NA	
Jejunum	X		X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*	X*	X*
Lacrimal gland					X	X	X
Larynx							
Liver	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X*	X*
Lymph nodes, cervical							
Lymph nodes (LALN)				X			X
Lymph nodes, mandibular	X		X		X	X	
Lymph nodes, mediastinalis							
Lymph nodes, mesenteric	X		X		X	X	
Mammary gland	X		X	X	X	X	
Nasal cavity							
Optic nerves			X				
Ovaries	X*		X*	X*	X*	X*	X*
Oviduct							
Pancreas	X	X	X	X	X	X	X
Parathyroid	X		X	X	X	X	X
Peripheral nerve				X			
Pharynx							
Pituitary	X*		X*	X*	X*	X*	X*
Prostate	X*		X*	X*	X*	X*	X*
Rectum							
Salivary gland	X*		X*	X*	X*	X*	X*
Sciatic nerve	X		X		X	X	
Seminal vesicles	X		X	X	X	X	X
Skeletal muscle	X		X	X	X	X	X
Skin	X		X	X	X	X	X
Spinal cord	X		X	X	X	X	X
Spleen	X*		X*	X*	X*	X*	X*
Stomach	X		X	X	X	X	X
Testes	X*		X*	X*	X*	X*	X*
Thoracic Limb	X						
Thymus	X*		X*	X*	X*	X*	X*
Thyroid	X*		X*	X*	X*	X*	X*
Tongue	X		X	X	X	X	X
Trachea	X		X	X	X	X	X
Urinary bladder	X		X	X	X	X	X
Uterus	X*		X*	X*	X*	X*	X*
Uterine horn							
Vagina	X		X	X	X	X	X

GENETIC TOXICOLOGY

Mouse bone marrow erythrocyte micronucleus study of SCH 34117

Schering Study No.: 97118 Report No.: P-6912 Volume: 21.7

Study Dates: Starting date 10/31/1997; report issued 11/19/1998
Testing Lab: Schering Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Lot No. 97-34117-X-02RA; purity = %) in 0.4% methylcellulose
GLP: The study was accompanied by a signed GLP compliance statement.
QA report: Yes.
Parameter: Clastogenicity

Methods: SCH 34117 was evaluated for its potential to induce micronuclei in the bone marrow of male and female CD-1 mice (6-8 weeks old; 20.1-32.1 g; 6/sex/dose/sacrifice time) following two consecutive daily intraperitoneal doses of 12.5, 25 or 50 mg/kg (dose volume: 5-20 ml/kg; concentrations: 2.5 mg/ml). Dose selection was based upon a dose-ranging study in which mice, administered two consecutive daily intraperitoneal doses of 2.5-40 mg/kg, exhibited reduced PCE/NCE ratio (10% compared to vehicle control animals) 72 hours following dosing and rough hair coat in males and one high-dose female was sacrificed on Day 4 due to severe clinical signs (rough hair coat, chromorrhinorrhea and hunched posture) and the PCE/NCE ratio was reduced by 29% compared to controls. Two trials were performed and mice were sacrificed at 24 hours after final dose in the first trial and 48 hours after final dose administration in the second trial; animals treated with positive control were sacrificed at 24 and 48 hours after dosing in trials 1 and 2, respectively. Bone marrow erythrocytes were removed from the femur of five mice from each dose group/sex and three bone marrow smears were prepared for each mouse. With two of those smears, a total of 2000 polychromatic erythrocytes (PCE) were screened for micronuclei. The micronucleus frequency of each dose for each sex was calculated from the total number of micronucleated PCE in 10000 PCE pooled from five mice and compared with that of the vehicle control. Micronucleated NCE were evaluated during the screening of micronuclei in 2000 PCE for each mouse and compared with vehicle controls. Bone marrow toxicity was evaluated by the PCE/NCE ratio from approximately 20 PCE in each mouse. A trial was considered to be valid if the micronucleus frequency in vehicle controls was in the normal range (0.08 to 0.5%); a significant increase of micronucleus frequency in the positive control group above the vehicle control group; and data was available from at least three mice from the vehicle and positive control groups and from each test article dose group. The test article was considered to have caused a positive response if the test article induces a statistically significant increase of micronucleus frequencies in PCE at two consecutive doses. Cyclophosphamide (50 and 30 mg/kg for Trial 1 and 2, respectively) was used as a positive control.

Results: In trial one and two, two high dose males mouse died on Days 3 and 4. Clinical signs were observed in mid-dose males and high-dose males and females (rough hair coat at 25 mg/kg; urogenital staining, hypoactivity, scant feces, salivation at 50 mg/kg). Bone marrow toxicity was noted in males at all doses at 24 hours as PCE/NCE ratios varied from 1.23 in vehicle controls to

0.88, 0.79 and 0.65 at the low- mid- and high-doses corresponding to decreases of 28.5, 35.8, and 47.2%. In females, bone marrow toxicity was noted only at the highest dose (37.6% reduction in PCE/NCE ratio). At 48 hours, bone marrow toxicity was noted in high-dose males and females (39.3% and 33.6% reduction in PCE/NCE ratio, respectively). There was no significant increase in micronucleus frequency at any dose in males or females. Cyclophosphamide induced a 19.8 to 19.9-fold and 10.6 to 15.7-fold increase of micronucleus frequency over the vehicle controls in trials one and two, respectively. The results indicate that SCH 34117 was negative under the conditions of this micronucleus assay, in concurrence with the sponsor's conclusion.

OVERALL SUMMARY AND EVALUATION

Multiple Dose Toxicology: Two 3-month oral gavage toxicity studies were performed with SCH 34117 in rats (3, 30, 60, and 120 mg/kg SCH 34117 and an active control of 120 mg/kg loratadine) and monkeys (6, 12, and 18/24 mg/kg SCH 34117 and an active control of 22/72 mg/kg loratadine) in order to support clinical studies and bridging to the chronic toxicology program performed for loratadine. The primary histological findings were indicative of systemic phospholipidosis and were found in organs and tissues throughout the body including the adrenals, brain, bone and bone marrow, epididymides, eyes, heart, kidneys, lymph nodes, liver, lungs, esophagus, ovaries, pancreas, parathyroid and pituitary glands, prostate, salivary glands, seminal vesicles, skeletal muscle, stomach, intestines, spleen, testes, thyroid, thymus, tongue, trachea, uterus, urinary bladder, and vagina. Findings were most severe at the high SCH 34117 dose, while findings at 60 mg/kg were comparable to those at 120 mg/kg loratadine. Loratadine showed greater induction potential of cytochrome P450 and PROD than SCH 34117. Plasma concentrations increased supra-proportionally and were greater in females than in males. Drug accumulation was also observed with multiple dose administration. NOAELs of 3 mg/kg and 30 mg/kg were identified for females and males, respectively. The observed toxicity profile is consistent with that observed in previous studies with SCH 34117 or loratadine. In monkeys, histopathological findings also included indicators of systemic phospholipidosis in organ systems throughout the body including lymph nodes, liver, lungs, pancreas, salivary glands, stomach, thymus and trachea. Anti-cholinergic effects were noted clinically. Previous studies in monkeys with SCH 34117 (2-weeks at doses up to 6.5 mg/kg, see Original IND Review, and 4-weeks at doses up to 12 mg/kg, see Review #2) did not demonstrate definitive target organs of toxicity, although thyroid hyperplasia in high-dose males and ovarian mineralization in high-dose females were observed in the 4-week study. Thyroid hyperplasia was not observed in the 3-month study. However, ovarian mineralization was noted in high-dose females as well as the active loratadine group. The sponsor has previously been asked submit histopathology data for this finding in low and mid-dose groups in the 28-day monkey study for determination of NOAELs and to clarify the term "mineralization" (see Review # 2), but has not done so. Overall, the toxicity profile at the high-dose of SCH 34117 was comparable to that observed following loratadine administration and mean systemic SCH 34117 exposure in the two groups was comparable. A NOAEL of 12 mg/kg was identified in this study.

Genetic Toxicology: An in vivo mouse bone marrow micronucleus assay with SCH 34117 was concluded to be negative. These findings are consistent with the results of an Ames assay and an in vitro chromosome aberration assay reported previously.

Carcinogenicity Assessment Waiver Request: The sponsor submitted a carcinogenicity waiver request which was presented before the Senior Pharmacology/Toxicology Policy Group. The sponsor's proposal for the waiver from performing carcinogenicity studies for SCH 34117 was based primarily on rat and mouse SCH 34117 exposures achieving at least a 25-fold rodent to human exposure multiple in previous carcinogenicity studies with loratadine. The Senior Policy Group concluded that SCH 34117 was adequately assessed for carcinogenicity in rats since the carcinogenicity study performed for loratadine resulted in an unbound SCH 34117-derived rodent to human exposure multiple which exceeded 25. However, the Policy Group concluded that a 2 year mouse carcinogenicity study with SCH 34117 should be performed as a Phase 4 commitment since neither appropriate SCH 34117 exposure multiples nor a maximum tolerated dose were achieved in the mouse carcinogenicity study performed with loratadine. See Attachments 1, 2, and 3 for more detailed information on the sponsor's proposal and the Policy Group's recommendations.

RECOMMENDATIONS

1. The similar toxicological findings following SCH 34117 and loratadine administration in rats and monkeys at similar exposure levels of SCH 34117 in the 3-month toxicology studies support bridging to the chronic loratadine toxicology program. Therefore, the sponsor will not be required to perform additional chronic toxicity studies with SCH 34117.
2. The sponsor is requested to provide clarification of the term mineralization (i.e., type of minerals) as related to the findings in the ovaries of monkeys (Study P-6976). A previous request for low-dose and mid-dose histopathology data for this finding in the 28-day monkey study (Study SN 980089) is no longer considered necessary as the finding was not instrumental in determining a NOAEL in the 3-month study.

Timothy J. McGovern, Ph.D., Pharmacologist

Attachment I.
Attachment II.
Attachment III.

Original IND 55,364

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/R. Nicklas
HFD-570/G. Trout
HFD-570/T.J. McGovern
HFD-540/B. Hill

Draft Comments for Letter to Sponsor:

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IND 55, 364**Drug Name:** Descarboethoxyloratadine**Sponsor:** Schering Plough Corporation**Date:** October 8, 1999**Amendment to DCL Carcinogenicity Waiver request**

Mouse carcinogenicity study: The Senior Pharmacology/Toxicology Policy Group previously agreed that the AUC criterion or the MTD was not achieved in the mouse carcinogenicity study performed with loratadine and therefore it should be performed with DCL.

Rat carcinogenicity study: Findings in a mouse lymphoma assay with loratadine were considered to be positive in the non-activation phase by the Genotoxicity Committee. The positive conclusion in this assay indicates that the carcinogenicity waiver request by the sponsor should be decided based upon MTD, as recommended by the Senior Pharmacology/Toxicology Policy Group, unless the sponsor performs an additional mouse lymphoma assay with negative results using DCL or if the sponsor demonstrates that DCL was adequately assessed in the activation phase of the mouse lymphoma assay performed previously with loratadine which produced negative findings. This amendment addresses whether DCL was assessed at adequate levels in the mouse lymphoma assay performed with loratadine based on interim data submitted by the sponsor and whether the DCL exposure in the rat carcinogenicity study performed with loratadine was at the MTD level based on findings in a 3-month bridging study with DCL.

Should either the assessment of DCL in the activation phase of the mouse lymphoma assay or the achievement of the DCL MTD in the rat carcinogenicity study with loratadine be considered valid, the Policy Group indicated that the rat carcinogenicity study performed with loratadine would be an adequate assessment of the carcinogenic liability of DCL. In addition, a 2 year mouse carcinogenicity study with loratadine would be required as a Phase 4 commitment.

In vitro conversion of loratadine to DCL

The sponsor submitted interim data intended to show that DCL was present in the activation phase of the original mouse lymphoma at adequate levels to assess its genotoxic potential in this assay. The following table submitted by the sponsor on Oct. 5, 1999 shows the percent conversion of loratadine to DCL and DCL-related metabolites (LC/MS characterization of ¹⁴C-loratadine) after a 2 hour incubation in a HEPES buffer medium with liver S9 fraction from Aroclor-induce rats. Greater exposure to DCL and metabolites would be expected in the four hour incubation period utilized in the mouse lymphoma assay, although the incubation medium was different for this assay.

Loratadine Concentration		To DCL			To DCL Metabolites	Total
µM	µg/ml	% Converted	µM	µg/ml	% Converted	% Converted
0.3	0.11	19	0.06	0.02	52	71
35	13.3	22	7.7	2.4	23	45
100	38	18	18	5.6	11	29
250	95	4	10	3.1	2	6

In the mouse lymphoma assay performed with loratadine, the maximum loratadine concentration in the activation phase was 30 µg/ml. Based on the above data, it could be expected that the exposure to DCL, based on an approximation of 20% conversion rate in the mouse lymphoma assay, was approximately 5 µg/ml with a potential increase due to a doubling of incubation time. Thus, although it appears that exposure to DCL did occur in the activation phase of the mouse lymphoma assay which produced negative results, it is not certain that the level of DCL was sufficient to adequately assess the genotoxic potential of DCL.

Assessment of MTD based on 3-month bridging study in rats.

In a 3-month bridging study performed in rats, death occurred at doses of 120 and 30 mg/kg DCL in males and females, respectively. The MTDs for males and females were selected as 30 and 3 mg/kg, respectively, due to reductions in body weight gain of 12 and 7%, respectively. In addition, histopathological findings consisted primarily of systemic phospholipidosis and included vacuolation, atrophy, and necrosis. These findings were evident in males and females at a dose of 30 mg/kg or greater.

Dose (mg SCH 34117/kg/day):	0	3	30	60	120	120 mg loratadine/kg/day
Mortality (n=10/group)						
Males	0	0	0	0	9	0
Females	0	0	2	6	10	6
Males						
% Δ from control		↓1	↓12	↓33	↓99*	-30
Females						
% Δ from control		↓7	↓33	↓73	↓139**	-62

*: Day 54.

** : Day 36.

The table below compares the DCL exposure following a 28 day dietary dose of 25 mg/kg loratadine in male rats, the high dose tested in the rat carcinogenicity study, and the DCL exposure at the MTDs following 9 week oral administration. This comparison shows that females were exposed to approximately 3.7 times the DCL MTD in the carcinogenicity study with loratadine. Male rats, however, were exposed to only one-fourth of the DCL MTD in the carcinogenicity study with loratadine. Although the DCL exposure level is based upon male rats, females generally are exposed to greater concentrations of DCL at comparable doses. Thus, the actual exposure multiple should be greater. A 21 day dietary rat study using a loratadine dose of 25 mg/kg produced AUC values of 8,820 and 15,100 ng.hr/ml in males and females, respectively, which would result in exposure multiples of about one-third and 8-fold, respectively. Therefore, female rats appear to have been tested at their DCL MTD in the loratadine carcinogenicity study while males appear to have achieved only one-third to one-fourth of the MTD.

Study	Rat carcinogenicity study with loratadine (25 mg/kg)		Rat 3 month bridging study with DCL	
	Males	Females	Males	Females
MTD dose (mg/kg)			30	3
DCL AUC (0-24 hr) (ng.hr/ml)	7017*		26100**	1890**
Exposure multiple***			0.26	3.71

*from 28 day dietary study

** blood sampling during week 9 of drug administration

*** DCL AUC from rat carcinogenicity study / DCL AUC from 3 month bridging study.

Since the typical cutoff for reduced body weight gain in selecting an MTD is 10%, extrapolation of DCL exposure in males from a dose of 30 mg/kg, which induced a 12% body weight gain reduction, to 25 mg/kg, estimated to induce a 10% body weight gain reduction assuming a linear relationship, would result in an AUC of 21,750 ng.hr/ml and an exposure multiple of approximately one-third to two-fifths of the MTD using the 28-day and 21-day dietary AUC data, respectively.

An additional approach is to consider that the toxicity profiles observed in the 3-month bridging study with DCL were comparable at a DCL dose of 60 mg/kg and a loratadine dose of 120 mg/kg. Likewise, the DCL AUC was similar at these doses. It could, therefore, be reasoned that the dose of 25 mg/kg loratadine used in the rat carcinogenicity study would be similar in terms of DCL exposure to a DCL dose of 12.5 mg/kg. The dose of 12.5 mg DCL/kg is one-half of the 25 mg DCL/kg estimated to be the MTD in males in the 3-month bridging study after extrapolating exposure data to a 10% reduction in body weight gain.

The sponsor argues that since the MTD was clearly achieved in the rat carcinogenicity study, and since the toxicity induced by loratadine is considered to be related to DCL, the DCL MTD was, therefore, achieved.

Questions to the ORM Senior Pharm/Tox Group

1. Do you agree that the genotoxic potential of DCL was adequately assessed in the mouse lymphoma assay performed with loratadine based upon the conversion data submitted by the sponsor?
2. Do you agree that the MTD was achieved in the rat carcinogenicity study for females?
3. Although it does not appear that the MTD was achieved in the rat carcinogenicity study for males, do you consider the level of DCL exposure (one-fourth to one-half the DCL MTD depending upon the approach taken) to be adequate in order to support the sponsor's waiver request?

Tim Mc Lane
10/8/99

**Senior Pharmacology/Toxicology Policy Group
September 14, 1999**

Policy Team Joseph DeGeorge, Ph.D., HFD-024, Assoc. Dir. for Pharmacology and Toxicology
Paul Andrews, Ph.D., ODE I
Joe Sun, Ph.D., ODE II
Dave Morse, Ph.D., ODE III
Abby Jacobs, Ph.D., ODE V
Timothy McGovern, Ph.D., HFD-570, Presenting Reviewer
Adele Seifried, M.S., Executive Secretary

Others present: Mark Vogel, Ph.D., HFD-570
Barbara Hill, Ph.D., HFD-540

The following information reflects a brief summary of the Group discussion and recommendations from the meeting of September 14, 1999 and subsequent informal communications. Detailed study information can be found in the individual review.

IND # 55,364

Drug Name: Descarboethoxyloratadine (DCL)
Sponsor: Schering-Plough Corporation

Background: DCL is the primary active metabolite of loratadine, an antihistamine approved in 1992 and intended for the treatment of seasonal allergic rhinitis. Carcinogenicity studies with loratadine demonstrated evidence of hepatic carcinogenicity in male mice and male and female rats. The findings in rats were considered to be equivocal. In addition, the mouse study was not considered to have achieved the maximum tolerated dose (MTD). The anticipated clinical dose of DCL is 5 mg per day and is expected to result in similar DCL exposure to that achieved following 10 mg of loratadine. The drug was negative in the in vitro Ames Assay, the human lymphocyte chromosomal aberration assay, and an in vivo mouse micronucleus assay. Loratadine was negative in all assays performed with the exception of the non-active phase of the mouse lymphoma assay. The sponsor has requested a waiver from performing carcinogenicity studies for DCL based upon DCL exposure ratios achieved during carcinogenicity studies performed with loratadine.

Evaluation of Sponsor's Request for carcinogenicity assessment waiver.

The sponsor's proposal for a waiver from performing carcinogenicity studies for DCL is based primarily on rat and mouse DCL exposures achieving at least a 25-fold rodent to human exposure multiple via two approaches. In the first approach, DCL exposure estimates (based on plasma DCL levels) calculated from carcinogenicity studies performed in rats and mice for loratadine resulted in rodent to human exposure multiples of 123 and 33, respectively, using total DCL, but only 111 and 13, respectively, when considering protein binding data. Although the exposure multiples achieved for the rat exceeded 25, the Policy Team did not consider this

approach to be appropriate due to the extensive metabolism observed with loratadine and DCL in addition to species differences in the ratios of specific metabolites.

A second approach proposed by the sponsor was based upon exposure to total drug-derived radioactivity from the rat and mouse carcinogenicity studies with loratadine. The sponsor suggested that loratadine-derived radioactivity exposure was applicable in this case since the majority of loratadine-specific metabolites are structurally similar to DCL-derived metabolites and would not be expected to be of increased carcinogenic or toxicologic risk. The Policy Team disagreed with this rationale. The Policy Team did, however, consider the use of DCL-derived radioactivity, to be an acceptable approach. This approach resulted in total DCL-derived rodent to human exposure multiples of 45 and 7 in rats and mice, respectively, and unbound DCL-derived rodent to human exposure multiples of 41 and 3 in rats and mice, respectively. Thus, the targeted 25-fold exposure ratio was achieved in the rat but not in the mouse.

The minor change in exposure multiples observed with the rat when comparing total and unbound drug exposure is due to similarities in calculated free fraction between rats and humans while the unbound fraction is 2 to 3-fold less in the mouse. The sponsor suggested that the use of protein binding data was not valid since there is no evidence that species differences in protein binding has any impact on pharmacokinetics or tissue exposure. The Policy Team, however, believed that the consideration of free drug fraction is appropriate. In addition, whether total or unbound drug exposure multiples are considered, the 25-fold exposure ratio is exceeded in the rat and is not achieved in the mouse.

The Policy Team recommended that the positive findings in the non-activation phase of the mouse lymphoma assay with loratadine be re-evaluated to confirm the conclusion under current criteria since a positive finding raises concerns about the potential genotoxicity of DCL and precludes the use of kinetic data in supporting the sponsor's waiver request. Should the mouse lymphoma assay with loratadine be considered negative, the team recommended accepting the sponsor's waiver request for the rat carcinogenicity study based upon kinetic data since the 25-fold exposure multiple was exceeded in this species. However, the sponsor should perform a traditional 2 year mouse carcinogenicity study in the same strain used in the loratadine study since appropriate DCL exposure multiples were not achieved in the carcinogenicity study with loratadine. This study may be performed as a Phase 4 commitment.

Should the mouse lymphoma assay performed with loratadine be concluded to be positive in the non-activation phase, the exposure ratio approach proposed by the sponsor should be considered only if DCL is tested and found to be negative in a mouse lymphoma assay or if the sponsor provides evidence that DCL was present and adequately tested in the activation phase of the previous study which produced negative results. Otherwise, the waiver request for the rat study should be considered on the basis of whether a DCL Maximum Tolerated Dose had been achieved in the carcinogenicity studies performed with loratadine. If DCL is determined to be negative in the mouse lymphoma assay, the waiver request for the rat study would be considered acceptable based upon the achieved exposure multiples discussed above. If DCL is considered to be positive or not adequately tested in the loratadine mouse lymphoma assay, the waiver

request for the rat study should be considered based on achievement of the DCL Maximum Tolerated Dose in the loratadine carcinogenicity studies.

Post meeting notes: A consult was forwarded to the Genetic Toxicology Committee in reference to the positive findings in the non-activation phase of the mouse lymphoma assay performed with loratadine. The Committee concluded that the assay was clearly positive in the non-activation phase of the assay. Thus, the scenario described in the previous paragraph is the recommended approach by the Policy Team.

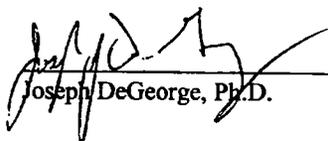
The sponsor submitted interim data intended to show that DCL was present in the activation phase of the original mouse lymphoma performed with loratadine at adequate levels to assess its genotoxic potential in this assay. The data indicated that the percent conversion of loratadine to DCL and DCL-related metabolites after a 2 hour incubation in a HEPES buffer medium with liver S9 fraction from Aroclor-induced rats was approximately 45%. Even greater exposure to DCL and metabolites would be expected in the four hour incubation period utilized in the mouse lymphoma assay, although the incubation medium was different for this assay. The Senior Policy Team considered this data and concluded that DCL had been adequately tested in the activation phase of the mouse lymphoma assay with loratadine which produced negative findings. Thus, the sponsor's waiver request could be considered based upon kinetic data.

Acceptability of the sponsor's waiver request for the rat carcinogenicity study based upon the achievement of MTD was also considered by the Policy Team. The Policy Team, however, did not accept this approach based on differences in the method of oral dosing (i.e., dietary in the loratadine carcinogenicity study and gavage in the three month bridging study with DCL).

ORM Pharmacology/Toxicology Senior Policy Team Recommendations and Conclusions

1. The Senior Policy Team concluded that DCL was adequately tested in the activation phase of the mouse lymphoma assay with loratadine which produced negative findings. Thus, the sponsor's waiver request for carcinogenicity studies can be considered based upon kinetic endpoints since the genotoxic battery for DCL was negative.
2. The rat carcinogenicity study performed with loratadine is acceptable in supporting the sponsor's waiver request since this study resulted in an unbound DCL-derived rodent to human exposure multiple which exceeded 25.

3. The sponsor's waiver request for the mouse carcinogenicity study is not acceptable since appropriate DCL exposure multiples were not achieved in the carcinogenicity study with loratadine and the mouse study with loratadine was not considered to have achieved the maximum tolerated dose. Thus, a 2 year mouse carcinogenicity study should be performed as a Phase 4 commitment. Positive findings in this study may necessitate further mechanistic explanation.

 Oct 19, 1999
Joseph DeGeorge, Ph.D.

cc:\n
/Division File HFD-570, IND 55,364
/HFD-570/McGovern/Sun/Trout
/ASeifried, HFD-024

**Background Package for Assessment of Proposal of Carcinogenicity Waiver Request
for Desloratadine**

IND No. 55,364

Sponsor: Schering-Plough Corporation

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

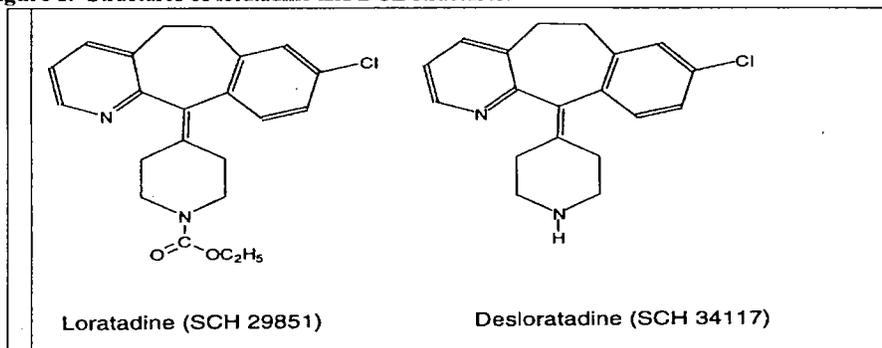
Indication: Allergic rhinitis/chronic idiopathic urticaria **Class:** Anti-histamine

Reviewer: Timothy J. McGovern, Ph.D.

Review Completed: 08 SEP 1999

Background: Descarboethoxyloratadine (DCL; SCH 34117) is the primary active metabolite of loratadine (Claritin), an antihistamine marketed in the US since 1993. The sponsor proposes that the carcinogenicity liability of DCL has been adequately addressed via the carcinogenicity studies conducted with loratadine using rats and mice. The sponsor suggests that the rodent to human DCL exposure ratio from the carcinogenicity studies performed in rats and mice for loratadine exceeds the ICH-recommended 25-fold factor whether exposure to DCL or to total drug-derived radioactivity is assessed. The sponsor further indicates that the similarities of DCL and loratadine in terms of pharmacology, pharmacokinetics, toxicity profile, genotoxicity, and reproductive toxicology support their proposal. Figure 1 shows the structures of the two compounds.

Figure 1. Structures of loratadine and DCL structures.



This background package will first briefly review the findings of the carcinogenicity studies performed in rats and mice, followed by a summary of the pre-clinical development work performed for DCL and a comparison to findings from related loratadine studies. Finally, a summary of the sponsor's proposal and rationale and this reviewer's recommendation will be presented.

Carcinogenicity studies with loratadine: Carcinogenicity studies with loratadine, performed in rats and mice, demonstrated evidence of hepatic carcinogenicity in male mice and male and female rats. A significant increase in liver adenomas in male mice at the high dose (40 mg/kg) and a dose-related increase in centrilobular hepatocellular hypertrophy was noted at doses of 12 and 40 mg/kg in male mice. In rats, slight increases in hepatocellular neoplasia in males at doses greater than or equal to 4 mg/kg and in female rats at a dose of 10 mg/kg were reported. The findings in rats were not statistically significant and were considered to be equivocal by the CAC. The mechanism of liver tumor induction is thought to be similar to that of phenobarbital, namely induction of P450 enzymes, and is not expected to be relevant in humans.

It should be noted that at a November, 1990 meeting of the CAC, members were in agreement that the MTD was not achieved in the mouse study. Opinion, however, was divided as to the usefulness of repeating a carcinogenicity study in mice.

Summary of the Pre-clinical Program with DCL:

Pharmacology and Safety Pharmacology: DCL shows similar pharmacological activity to loratadine with a relative oral potency in animals that is 2-8.5 times greater than loratadine. In vitro radioligand binding studies and functional H₁-antagonism studies on isolated guinea pig ileum have shown that DCL is up to 20 times more potent than loratadine. In vitro and in vivo studies also suggest that DCL, like loratadine, does not possess significant cardiovascular activity.

Pharmacokinetics: Following 2-week DCL administration in rats and monkeys, plasma DCL levels increased with increasing dose either proportionally or supra-proportionally. There was some indication of drug accumulation but this was not consistent at all doses or in both genders. Table 1 summarizes comparative DCL exposure in rats, monkeys and humans. Elimination half-life ranged from 2-4 hours in rats to 7.5 to 12 hours in monkeys. The metabolism of SCH 34117 is comparable to its parent, loratadine, which is metabolized to SCH 34117 via the removal of the ethyl carbamate group. The overall primary metabolites are 3-, 5-, and 6-hydroxy desloratadine with the 3-hydroxy desloratadine predominant in humans and the 5- and 6-hydroxy desloratadine predominant in animals. Excretion was primarily through the feces, although a significant portion is also excreted in the urine. Following administration of loratadine, DCL exposure was 4-8-fold greater than loratadine exposure in rats and monkeys. DCL exposure increased with repeated administration while loratadine exposure decreased.

Table 1: Comparative AUC following oral DCL administration.

Species	# of Doses	Dose	AUC
Rats	1	8 mg/kg	2027
	10		2421
Monkeys	1	6.5 mg/kg	3172
	14		5112
Humans	10	5 mg	57

Toxicity profile: The toxicity profile of DCL was evaluated in rats and monkeys in acute, 2-week, 1-month and 3-month toxicology studies. In each of the repeat dose studies, the sponsor included loratadine as an active control. The 3-month toxicology studies demonstrated that the toxicity profile of DCL is consistent with that of loratadine. Findings were primarily related to systemic phospholipidosis with inflammation and necrotic/degenerative changes observed at high doses which provide an adequate safety margin compared to the anticipated clinical dose. Increased potency of DCL compared to loratadine on a mg/kg basis appear to be explained by greater systemic exposure levels of DCL achieved following DCL administration compared to those achieved after a comparable dose of loratadine. The Division has concluded that no further general toxicology studies are necessary for the approval of DCL, pending submission of toxicokinetic data from the 3-month toxicity studies.

Enzyme induction: Liver tumors observed in rats and mice following chronic administration of loratadine are considered to be related to hepatic enzyme induction of the test drug. Table 2 shows the pertinent findings with loratadine obtained during the development of this drug which show that loratadine is a weak enzyme inducer.

Table 2: Inductive effects of loratadine (10 daily 100 mg/kg doses) in rats compared to phenobarbital.

Parameter	Control	Loratadine	Phenobarbital
Liver weight (g)	10.8	12.8	15.5
Liver/body wt (x100)	4.3	5.3	6
Microsomal proteins (mg/g liver)	35.6	44.7	42.2
Cytoch P450 (nmol/mg micr. prot.)	0.7	0.1	3.1
Aniline hydroxylase			
Nmol/min/mg micros prot	0.7	0.6	1.1
Nmol/min/g liver	24.7	27.1	46.2
Nmol/min/total liver	266.4	346.7	714.9
Benzphetamine N-demethylase			
Nmol/min/mg micros prot	2.5	2.6	4.1
Nmol/min/g liver	87.5	116.2	170.9
Nmol/min/total liver	944.2	1473.7	2644.5
Hexobarbital sleep time	27.2	27.3	6.1

Shaded values indicate significant increase compared to control values.

In 14- and 28-day toxicity studies in rats and monkeys conducted for the DCL program, evidence suggestive of slight enzyme induction was observed but was generally less than that induced by an equimolar dose of loratadine and was not statistically significant in rats (Table 3). There was no effect on liver weight in these studies, although liver weight was increased by 56% in males treated with 120 mg/kg DCL for 1 month; no effect in females was noted. Thus, the P450 enzyme inducing potential of DCL in the liver remains unclear.

Table 3: Enzyme induction increase (versus control values) following administration of DCL and equimolar dose of loratadine.

Species	Duration	Enzyme	8 mg/kg DCL	10 mg/kg Loratadine
Rat	14 days	PROD	2.8-fold	6.2-fold
			1.5-fold	2.3-fold
		EROD	1.32-fold	1.5-fold
			1.12-fold	1.12-fold
Monkey		PROD	1.7-fold	2.2-fold
			1.8-fold	1.6-fold
		EROD	1.9-fold	2.2-fold
			4.0-fold	3.0-fold

8' > AUC, slightly

Shaded values indicate significant increase compared to control values.

Genetic Toxicology: DCL produced negative results in the bacterial mutation test, the chromosome aberration assay in cultured whole blood human lymphocytes, and the in vivo mouse micronucleus assay. These findings are consistent with those observed with loratadine which was negative in a variety of assays but showed activity in the non-active phase of the mouse lymphoma assay (although at a drug level which induced excessively high cytotoxicity).

Sponsor's proposal:

The sponsor's proposal for a waiver for performing carcinogenicity studies for DCL is based primarily upon rat and mouse drug exposures which, they suggest, achieve rodent to human exposure multiples of at least 25 via two approaches: DCL exposure estimates and exposure to total drug derived radioactivity calculated from carcinogenicity studies performed in rats and mice for loratadine. These two approaches are presented below:

DCL Exposure:

Table 4 summarizes the DCL exposure of mice and rats in the loratadine carcinogenicity studies at doses of 40 mg/kg and 25 mg/kg, respectively, and 10 day dosing of human volunteers with 5 mg DCL based on protein binding data.

Table 4: Comparative DCL exposure and protein binding.

Species	Protein binding		DCL AUC (total drug)	Rodent/human Multiple (total)	DCL AUC (Free drug)	Rodent/human Multiple (free)
	Plasma Conc. (ng/ml)	% bound				
Mouse	100	94.7	1861	33	99	13
Rat	400	87.5	7017	123	877	111
Human	5-20	86.2	57	-	7.9	-

As this data demonstrates, an adequate rodent to human DCL exposure ratio (123 and 33) is achieved in both rats and mice based upon total DCL exposure. However, when protein binding is considered, the rodent to human DCL exposure ratio falls to 111 and 13, respectively, in rats and mice.

While use of free fraction brings the mouse to human exposure multiple to below 25-fold, the sponsor suggests that the use of free fraction is not appropriate since there is no evidence that the minor difference between plasma protein data of DCL in mouse, rat and humans has any impact on the pharmacokinetics or tissue exposure. Since the implied impact of protein binding is on drug distribution, the sponsor assessed volume of distribution and found that this is not accurately predicted across species by the extent of protein binding of DCL (Table 5). Overall, volume of distribution was high across species and higher in the mouse than in the rat, implying that protein binding did not interfere with drug distribution. Assuming comparable tissue binding, the mouse would actually be exposed to higher concentrations of DCL. Lower AUC in mouse may at least be partially attributable to the greater DCL distribution into mouse tissue. Thus, the sponsor concludes that ICH recommends using scientific judgement in making AUC comparisons and that the use of total drug concentration is permitted, especially since DCL is not highly bound in any of the species tested.

Table 5: Comparative relationship of protein binding and volume of distribution.

Species	Plasma protein Binding (%)	Vd/F* (L/kg)	Vd ** (L/kg)
Mouse	91.9-95.8	15.1	ND
Rat	87.5-92.3	9.9	8.2
Monkey	85.1-87.5	38.4	37.3
Human	82.8-86.2	51.1	ND

* oral administration **IV administration ND: not determined

While the sponsor indicates that there is no relationship between plasma protein binding and volume of distribution, there does appear to be a trend, with the exception of the rat, of increasing volume of distribution with decreased protein binding. Thus, this data suggests that protein binding data should be taken into consideration when determining the rodent to human exposure ratios. Therefore, the use of DCL exposure does not provide an adequate exposure ratio in mice.

Total drug-derived radioactivity:

Following administration of loratadine or DCL, only a small portion of circulating material across species is actually loratadine or DCL (DCL AUC/total ¹⁴C ratio of 0.04 to 0.13 following loratadine administration; DCL AUC/total ¹⁴C ratio of 0.08 to 0.37 following DCL administration). Therefore, a better approach in assessing rodent to human exposure multiples from the rat and mouse carcinogenicity studies with loratadine is to consider exposure to DCL and DCL-derived material based upon the fraction of total drug-derived radioactivity related to DCL and metabolites. This approach is supported by studies showing that all DCL-related

metabolites are detectable after loratadine administration and that a major portion of DCL metabolites formed in all species (37-53% of the dose for 3-, 5- and 6-hydroxydesloratadine) are biologically active.

Table 6 summarizes rodent to human exposure multiples based upon rodent exposure to DCL and metabolite-related radioactivity in the carcinogenicity studies performed for loratadine. This type of assessment achieves a greater than 25-fold exposure multiple for rats but falls well below that level for mice whether total or free drug-derived radioactivity is considered. However, one weakness with this approach is the assumption that DCL formed in vivo through the breakdown of loratadine results in a similar quantitative and qualitative metabolite profile as would occur if DCL were administered directly. Thus, the rodent to human exposure multiples characterized in Table 6 may not be accurate and could potentially be less than those estimated by the sponsor. While chromatograms submitted by the sponsor appear suggest that the predominant exposure in rats following loratadine administration is to DCL and its metabolites, the relationship is not as strong in mice.

Table 6: Rodent to human exposure multiples based upon DCL-derived radioactivity.

Species	Administered Drug	DCL/ ¹⁴ C Ratio*	AUC (ng.hr/ml)**		Rodent/human Multiple****	
			DCL	DCL + DCL metabolites***	Total	Free
Mouse	Loratadine	0.37	1861	5030	7	3
Rat	Loratadine	0.22	7017	31895	45	41
Human	DCL	0.08	57	713	-	-

* ratio of plasma DCL/total radioactivity after DCL administration; fraction of plasma radioactivity due to DCL.

** DCL exposure achieved in mouse and rat carcinogenicity studies (40 and 25 mg/kg loratadine) or in humans at steady state following multiple doses of 5 mg DCL/day.

***Calculated using DCL AUC and DCL/¹⁴C ratio (DCL AUC / DCL/¹⁴C ratio)

****Calculated by dividing rodent DCL + DCL metabolite AUC by human DCL + DCL metabolite AUC

Independent of our concerns with this approach, the sponsor feels that the magnitude of the carcinogenicity safety margin obtained in the loratadine carcinogenicity studies is significantly understated since this approach does not consider loratadine-specific metabolites that might be formed through non DCL-related metabolic pathways but could share potential carcinogenic liabilities with analogous DCL metabolites. They propose that the exposure multiple should be based on the exposure to total drug-derived material achieved in rodents in the loratadine carcinogenicity studies and in humans following administration of DCL. Many of the loratadine-specific metabolites as well as the DCL-related metabolites are hydroxylated or oxygenated products of the tricyclic ring portion of the molecule contained in both loratadine and DCL. These metabolites are listed in Table 7, in which lines 2-15 are loratadine specific metabolites and lines 16-47 are detected regardless of administration of DCL or loratadine.

Table 7: Cross species metabolism of loratadine and DCL.

Table 11 Cross-Species Comparison and Relative Contribution of Loratadine and Desloratadine Metabolites					
	Metabolites/Parent	Mouse	Rat	Monkey	Human
1	SCH 29851	+	++	++	++
2	3-OH-SCH 29851	++	+	++	
3	5-OH-SCH 29851	++	+	+	+
4	6-OH-SCH 29851	++	+	+	+
5	dihydroxy-SCH 29851	+	++	+	
6	3-OH-SCH 29851-glucuronide	+++		++	+
7	5-OH-SCH 29851-glucuronide	+		+	
8	6-OH-SCH 29851-glucuronide	+		+	
9	hydroxy-SCH 29851-glucuronide(s)			+++	
10	dihydroxy-SCH 29851-glucuronide(s) (28-30 min)	+			
11	dihydroxy-SCH 29851-glucuronide(s) (12-22 min)			++	++
12	SCH 29851-ketone		+		
13	Metabolite H (SCH 29851-COOH)		++		
14	Unknown I ₁ (hydroxy-SCH 29851-COOH)		++		
15	Unknown I ₂ (hydroxy-SCH 29851-COOH)		++		
16	SCH 34117	+++	+++	+++	+++
17	SCH 39090 (6-OH-SCH 34117)	++	+++	+++	++
18	SCH 39091 (5-OH-SCH 34117)	+++	+++	+++	++
19	SCH 45581 (3-OH-SCH 34117)	+	+	+	+++
20	SCH 218985 (5,6-di-OH-SCH 34117)		++		
21	SCH 356467 (C11-Pyridine)		+		
22	SCH 357130 (C11-Pyridine-N-Oxide)	+	+++		
23	dihydroxy-SCH 34117		+	+	
24	SCH 39090-glucuronide			++	
25	SCH 39091-glucuronide			+++	
26	SCH 45581-glucuronide	+	+	+	++++
27	hydroxy-SCH 34117-glucuronide(s) (6-12 min)		+	++	++
28	hydroxy-SCH 34117-glucuronide(s) (18-27 min)		+	++	
29	dihydroxy-SCH 34117-glucuronide(s) (11-14 min)			+	++
30	dihydroxy-SCH 34117-glucuronide(s) (12-18 min)		+		
31	monoxy-SCH 34117-glucuronide			+++	
32	Unknown C ₁ (hydroxy-SCH 357130)	+	++	+	
33	Unknown C ₂ (hydroxy-SCH 357130)		++	+	
34	Unknown C ₃ (hydroxy-SCH 357130)	+	+	+	
35	Unknown C ₄ (hydroxy-SCH 357130)	+	+	+	
36	Unknown C ₅ (hydroxy-SCH 357130)		+	+	
37	Unknown C ₆ (hydroxy-SCH 357130)	+	+		
38	Unknown F ₁ (2'-Oxo-SCH 34117)	+	+	+	+
39	Unknown F ₂ (2'-Oxo-SCH 34117)	+	+	+	+
40	Unknown G ₁ (hydroxy-SCH 356467)		+		
41	Unknown G ₂ (hydroxy-SCH 356467)		+		
42	Unknown G ₃ (hydroxy-SCH 356467)		++		
43	Unknown G ₄ (hydroxy-SCH 356467)		+		
44	Unknown K ₁ (hydroxy-Unknown F)	+	+	+	+
45	Unknown K ₂ (hydroxy-Unknown F)	+	+	+	+
46	Unknown K ₃ (hydroxy-Unknown F)	+	+	+	+
47	Unknown K-glucuronide(s)	+		+	+

All loratadine-specific metabolites in mice have analogous DCL metabolites which have been detected in mouse, rat, monkey and human as shown in Table 8. The numbers beside each structure correspond to the numbers on the left hand column of Table 7.

Table 8: Loratadine-specific mouse metabolites and analogous DCL metabolites.

Table 15 Loratadine-Specific Mouse Metabolites and Analogous Desloratadine Metabolites			
Loratadine-Specific Metabolite		Analogous Desloratadine Metabolite	
No.^a	Structure	No.^a	Structure
2		19	
3		18	
4		17	
5		20 ^b and/ or 23 ^{b,c}	
6		26	
7		25 ^c	
8		24 ^d	
10		29 ^{b,d} and/ or 30 ^b	

a: Number corresponds to metabolite/parent number in Table 11
b: Rat metabolite
c: Monkey metabolite
d: Human metabolite

Only loratadine metabolites in which the ethyl carbamate group is oxidized in the rat have no corresponding DCL analogs as shown in Table 9.

Table 9: Loratadine specific rat metabolites and analogous DCL metabolites.

Table 16 Loratadine-Specific Rat Metabolites and Analogous Desloratadine Metabolites			
Loratadine-Specific Metabolite		Analogous Desloratadine Metabolite	
No.^a	Structure	No.^a	Structure
2		19	
3		18	
4		17	
5		23	
12		38 and/ or 39	
13			None
14 and/ or 15			None

a: Number corresponds to metabolite/parent number in Table 11

The sponsor, therefore, suggests that the analogous metabolites of DCL and loratadine might share reactive sites and/or reactive propensities. Based upon structural similarities of DCL and loratadine and corresponding metabolites, it is likely that metabolic oxidations in the tricyclic ring occur in same manner by the same enzymatic processes. For example, the primary known metabolites of both DCL and loratadine arise from oxidation of the C-3 position of the pyridine and the C-5 and C-6 positions of the bridgehead. It is anticipated that the analogous metabolites share similar chemical reactivity towards oxidative enzymes. Thus, they conclude that estimation of rodent to human exposure based on grouping of metabolites is appropriate. The results of this approach are summarized in Table 10 and suggest that adequate rodent to human exposure multiples are achieved in both rats and mice regardless of whether total or free drug is considered.

Table 10: Rodent to human exposure multiples based upon total drug-derived radioactivity.

Species	Administered Drug	DCL/ ¹⁴ C Ratio*	AUC (ng.hr/ml)		Rodent/human Multiple****	
			DCL**	¹⁴ C ***	Total	Unbound
Mouse	Loratadine	0.04	1861	46525	65	25
Rat	Loratadine	0.13	7017	53977	76	69
Human	DCL	0.08	57	713	-	-

* ratio of plasma DCL/total radioactivity after loratadine administration; fraction of plasma radioactivity due to DCL.

** DCL exposure achieved in mouse and rat carcinogenicity studies (40 and 25 mg/kg loratadine) or in humans at steady state following multiple doses of 5 mg DCL/day.

*** Calculated using DCL AUC and DCL/¹⁴C ratio (DCL AUC / DCL/¹⁴C ratio)

**** Calculated by dividing rodent ¹⁴C ratio by human ¹⁴C ratio.

While the sponsor is correct in that loratadine-related and DCL-related metabolites are structurally similar, there is currently no evidence available concerning the relative potency of the respective metabolites or protein binding. Their estimation includes an assumption that protein binding of the metabolites is equivalent to that observed with DCL. Also, since DCL has been shown to have greater potency than loratadine, it is not unreasonable to expect that biologically active metabolites of DCL, such as 3-, 5-, and 6-hydroxydesloratadine, may have greater activity than analogous loratadine-related metabolites.

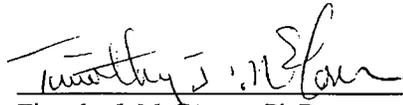
Reviewer's Assessment

Of the two approaches proposed by the sponsor to assess the exposure ratios achieved in the loratadine carcinogenicity studies, the second approach is considered to be the most appropriate due to the high degree of metabolism that occurs. However, this approach also has disadvantages in that assessment of DCL-derived exposure assumes that DCL is metabolized similarly whether administered as loratadine or DCL. Meanwhile, assessment of the exposure ratio based upon total drug-derived radioactivity assumes that loratadine-specific metabolites equally predict the toxicity and carcinogenicity potential of DCL. Regardless of the approach taken by the sponsor, the rat to human exposure ratio exceeds the 25-fold exposure ratio recommended by ICH. However, the validity of the different approaches remains unclear. In

mice, only the approach based upon total drug-derived radioactivity achieves the 25-fold ratio. Additional factors in deciding whether to grant the carcinogenicity waiver are DCL's similarity to loratadine in terms of the negative results in the genotoxicity battery (with the exception of loratadine's activity in the non-active phase of the mouse lymphoma assay at a drug level which induced high cytotoxicity) and its possible P450 enzyme induction.

Questions to the ORM Senior Pharm/Tox Team

1. Do you agree that the carcinogenicity study performed in rats with loratadine adequately assesses the carcinogenic liability of DCL? If not, what further studies can the sponsor perform to address the deficiencies?
2. Do you agree that the carcinogenicity study performed in mice with loratadine adequately assesses the carcinogenic liability of DCL? If not, what further studies can the sponsor perform to address the deficiencies?
3. If you agree that the carcinogenicity studies performed with loratadine adequately assess the carcinogenicity potential of DCL, has the sponsor adequately shown that DCL operates via a similar P450 enzyme inducing mechanism based upon the data provided by the sponsor? If not, what further studies of this mechanism or others can the sponsor perform to address the deficiencies?

 9/8/99

Timothy J. McGovern, Ph.D.
Reviewing Pharmacologist

Preclinical Studies Submitted and Reviewed in this IND:

Study	Serial No.	Report #	Volume
Pharmacokinetics and Toxicokinetics:			
TK of single oral doses of SCH 34117 or 29851 in cynomolgus monkeys	031	SN 97525	2
Multiple Dose Toxicology:			
Draft clinical/gross necropsy tables from 3-mos monkey toxicology study	032	SN 98212	1
Reproductive Toxicology:			
Pilot perinatal and post-natal development study in rats	031	SN 97512	1

Studies Not Reviewed in this IND: None.

Studies Previously Reviewed: None

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

PHARMACOKINETICS and TOXICOKINETICS

Cynomolgus monkeys were administered a single dose of SCH 34117 (11.75 or 23.5 mg/kg) or loratadine (24, 160 or 320 mg/kg) by oral gavage (5 ml/kg, 2.35-64 mg/ml). Blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24 and 36 hours after dosing. All monkeys survived the dosing and observation period with no test-article or study-related clinical signs reported. Following administration of SCH 34117, exposure parameters increased in a proportional manner (Table 1) and T_{max} was achieved at approximately 4 hours. The AUC was approximately twice as great in females than in males. Following loratadine administration, the T_{max} for SCH 34117 was 1.5 to 6-fold greater than that reported for direct administration of SCH 34117 and tended to increase with dose. Exposure to SCH 34117 increased sub-proportionally from the low to mid-dose and then plateaued, possibly due to saturation. A dose of 24 mg/kg loratadine resulted in a SCH 34117 C_{max} which was ~ 52% and 75% less in males and females, respectively, than that observed in animals administered a similar dose of SCH 34117. Systemic exposure was also reduced by ~ 27% and 66%. Exposures to SCH 34117 were roughly similar in groups administered 11.75 mg/kg SCH 34117 and 24 mg/kg loratadine, and groups administered 23.5 mg/kg SCH 34117, 160 mg/kg loratadine and 320 mg/kg loratadine. Females continued to demonstrate greater exposure levels, though not as dramatically as when SCH 34117 was administered directly. Exposure to loratadine following loratadine administration was significantly less than exposure to SCH 34117 (~33-90%) and also increased sub-proportionally from the low to mid-dose and before plateauing from the mid- to high-dose. T_{max} was between 2 and 4 hours.

Table 1. Pharmacokinetics of SCH 34117 and loratadine following single oral gavage dosing.

Mean SCH 34117 parameters after SCH 34117 or loratadine administration										
Parameter	11.75 mg/kg SCH 34117		23.5 mg/kg SCH 34117		24 mg/kg loratadine		160 mg/kg loratadine		320 mg/kg loratadine	
	Male n=3	Female n=3	Male n=3	Female n=3	Male n=3	Female n=3	Male n=3	Female n=3	Male n=3	Female n=2
Cmax (ng/ml)	277	454	604	1355	290	341	594	1028	663	692
Tmax (hr)	4	3.3	4	4	11.3	6.7	11.3	19.3	23.3	24
AUC _(0-36 hrs) (ng.hr/ml)	4778	8018	11258	22818	7137	7760	14003	29293	18007	19892
Mean loratadine parameters after loratadine administration										
Cmax (ng/ml)					178	382	726	694	739	522
Tmax (hr)					2.3	2	3.3	4	4	2
AUC _(0-36 hrs) (ng.hr/ml)					708	1644	3808	6994	6802	4529

A previously submitted 14-day study in monkeys, which were administered lower doses of SCH 34117 (1.6-6.5 mg/kg) and loratadine (8 mg/kg), demonstrated significantly increased exposure levels in males at doses of 1.6 and 3.2 mg/kg compared to females, and similar exposure levels in both sexes at the high dose of 6.5 mg/kg, on Days 1 and 14. Reported AUCs increased sub-proportionally in males and proportionally (low to mid-dose) and supra-proportionally (mid to high-dose) in females; the Tmax on Day 1 (2.5-4 hours) was similar to that observed presently. In addition, the SCH 34117 AUC increased proportionally on Day 1 and sub-proportionally on Day 14 of a 28-day study in monkeys which were administered SCH 34117 (3-12 mg/kg) and loratadine (12 mg/kg); SCH 34117 Tmax was reported as 1.5 to 4 hours. An overall comparison of the resultant Day 1 AUCs from the three studies submitted to date demonstrate a dose-proportional increase from 1.6-12 mg/kg, although some variability is present.

TOXICOLOGY

MULTIPLE-DOSE TOXICITY:

Monkey, 3-Month Oral (Gavage) Toxicity (Draft Tables)

Study No.: N003134G Study No.: 98212 Volume: 1

Study Dates: Starting date; not provided; report issued: not applicable
 Testing Lab:
 Test Article: SCH 34117 (Batch & purity not reported)
 Concentration: Not reported.
 Dose Volume: Not reported.
 GLP: This report was unaudited.
 QA report: No.

Methods: Cynomolgus monkeys were assigned to the following treatment groups:

Dose	0	6	12	18/24*	22/72* mg loratadine/kg/day
(mg SCH 34117 /kg/day):					
No./sex	4	4	4	4	4

*: Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months.

Results: Results are summarized in tables 2-3.

Mortality: None reported.

Clinical Observations: Anti-cholinergic effects were the primary drug-related clinical observations in this study (Table 2). These included few or no feces at the mid- and high-dose of SCH 34117 and loratadine-treated animals. A slight increase in the incidence of extended abdomen and hunched posture were also noted in these groups. Various findings unique to the loratadine-treated animals were also reported.

Table 2. Clinical observations in monkeys following 3-month administration of SCH 34117.

Observation	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - loratadine	0	6	12	18/24	22/72 - loratadine
Abrasion - foot					1					
- head					1					
- mouth								1		
Alopecia - arm					1			2		
- body					1		1	1		
- head					1	1	1	1		
- leg					2			1		
- shoulder					1		1			
Emesis			1	2		1		1	1	
Feces - few				4	1				2	3
Feces - none				4	2			1	3	2
Feces - mucoid										1
Discoloration - body				1						
Extended abdomen				1	1					2
Hunched posture				1	1					1
Lethargic					1					1
Swelling - foot									1	
- leg									1	

Few feces: first observed days 71-80 (F) and 66-71(M). F: lasted for 1 d at HD 34117, 11 d at 22 L. M: 14 d at HD 34117, 26 d at 22 L.

No feces: first observed days 72-83 (F) and 78-84 (M). F: lasted for 1 d at MD 34117, 5 d at HD 34117, and 1 d at 22 L. M: 3 d at HD 34117, 8 d at 22 L.

Gross Pathology: The primary gross findings included dilatation of the cecum and colon which are likely related to the decreased fecal excretion noted above (Table 3). There was also a slight increase in dilatation of other organs of the digestive system in 1 loratadine-treated female.

Table 3. Gross observations in monkeys following 3-month oral administration.

Observation	Males					Females				
	Dose (mg/kg)					Dose (mg/kg)				
	0	6	12	18/24	22/72 - loratadine	0	6	12	18	22/72 - loratadine
Cecum - dilatation				2	2		1		1	2
Colon - dilatation				2	2		1		1	2
Duodenum - dilatation										1
Ileum - dilatation										1
Jejunum - dilatation										1
Stomach - dilatation										1
Heart - focus									1	
Spleen - adhesion					1					
- deformity					1					

A NOAEL could not be identified in this study since only draft tables for clinical observations and gross pathology were submitted. The sponsor was informed via telephone that a final decision as to whether this study would support the sponsor's bridging strategy for this development program must await submission and review of the histopathology and toxicokinetic data.

REPRODUCTIVE TOXICOLOGY

Rat (oral) Pilot Perinatal and Postnatal Development Study

Report No.: P-6817 Study No.: 97512 Volume: 9.1

Study Dates: Starting date 11/25/97; report issued 7/10/98
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-34117-X-02RA; purity not reported) in 0.4% (w/v) aqueous methylcellulose
Concentration: 0.6-3.6 mg SCH 34117/ml
Dose Volume: 5 ml/kg/day
GLP: The study was an unaudited report.
QA report: No.

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

Dose (mg /kg/day):	0	3	9	18
No./dose group	5	5	5	5

Each female was placed with a male rat from the same strain and supplier. Cohabitation continued until positive evidence of mating was observed. Females were then dosed once daily by esophageal intubation (gavage) from pregnancy Day 6 through lactation Day 7. The following observations were made:

Clinical observation . . Dams examined daily
 Body weight Dams weighed on pregnancy days 0, 6, 9, 12, 15, 18, and 21, and on lactation days 1, 4, and 7.
 F₀ parturition Observed beginning day 21 of pregnancy for abnormal labor, nursing, or nesting behavior.
 Necropsy Lactation Day 7, examined for external and visceral changes, and implantation site.
 Litter size total numbers of live and dead offspring recorded daily for each litter until lactation Day 7. Pup survival calculated on lactation Days 0, 1-4, and 5-7.
 Sex determination Offspring sexed externally on lactation Days 0 and 7
 External examination/ Appearance & behavior . Offspring examined daily from lactation Day 0 through 7.
 Body weight Offspring weighed on lactation days 0, 4, and 7.
 Necropsy Offspring sacrificed on lactation Day 7, examined for external and visceral changes

Results:

Mortality: All dams survived until scheduled sacrifice.

Clinical signs: Large fecal pellets, likely related to the anti-cholinergic effects of the drug, were observed in the SCH 34117-treated groups. The large pellets were observed in 3 of 5 low-dose, 5 of 5 mid-dose, and 3 of 5 high-dose animals and occurred primarily between gestation days 8 and 21.

Body weight (F₀): Overall mean maternal body weight was not significantly affected in any treatment group. However, mean body weight gain for high-dose dams was statistically lower (48%) than control animals during gestation days 6 through 12 (Table 4). Body weight gain in the low- and mid-dose groups was also reduced (not statistically significant) by 8 and 28%, respectively. This finding is considered to be treatment-related since similar findings were observed in an embryo-fetal developmental toxicity study in rats (Report # 6718; reviewed in Original IND Review) at doses of 24 and 48 mg/kg (52 and 72% reduction, respectively). On Day 21 of gestation, body weight gain compared to controls was reduced by 9% in the high-dose group, similar to the other treatment groups. By Day 7 of the lactation period, however, body weight gain in the high dose group was increased by 7%, while body weight gain continued to be reduced in the low and mid-dose groups by 33 and 47%, respectively.

Table 4. Body weight gain (% change vs control) in animals administered SCH 34117.

Dose group (mg/kg)	Type of treatment			
	Gestation Days 6-12	Gestation Day 12	Gestation Day 21	Lactation Day 7
3	↓8%	↓10	↓15%	↓33%
9	↓28%	↓24	↓16%	↓47%
18	↓48%	↓6	↓9%	↑7%

Shaded areas indicate statistically significant difference from control.

F₀ parturition: No SCH 34117-related effects on pregnancy or labor.

Necropsy (F₀ generation): No treatment-related findings were observed. One low-dose rat had a thickened uterine wall.

F₁ survival: No treatment-related effects were observed. The percentages of dying pups were similar between control and drug treatment groups.

Body weight (F₁): Although mean pup weights in SCH 34117-dosed groups were not statistically different from control values, high-dose pup weights were consistently lower than control values (7-11%). Reduced pup weights (9%) were also observed in an embryo-fetal developmental toxicity study in rats at doses of 24 mg/kg or greater.

Necropsy (F₁ generation): All pups were grossly normal.

A dose of 18 mg/kg induced a significant decrease in maternal body weight gain in the present study. Based on available pharmacokinetic data and assuming dose-proportional increases in systemic exposure, this dose provides an estimated 80-fold exposure ratio compared to the proposed clinical dose of 7.5 mg SCH 34117. A previous embryo-fetal developmental study also demonstrated similar effects with shorter dosing duration at doses of 24-48 mg/kg. Thus, the oral high-dose in the definitive perinatal and postnatal study in rats should be 18 mg/kg, in concurrence with the Sponsor's conclusion.

OVERALL SUMMARY AND EVALUATION

The Sponsor submitted a single oral (gavage) dose toxicokinetic study and draft tables of clinical and gross histopathology data from a 3-month study in monkeys, and a pilot Segment II study in rats. The Sponsor had requested Division feedback as to whether the submitted data from the 3-month monkey study was sufficient to preclude the Sponsor from performing an additional 3-month study in monkeys in order to adequately describe the toxicity profile of SCH 34117 for the purpose of the Sponsor's bridging strategy to the development program for loratadine. However, clinical signs are not an adequate indicator of toxicity profile without other parameters such as histopathology. Thus, the limited nature of this submission preclude the Division from reaching a conclusion on this issue at this time. The Sponsor has been contacted by the Project Manager (see notes of teleconference of 12/10/98) and informed that a final decision on this issue must await submission of the histopathology and PK/TK data. In addition, the Sponsor's proposed oral high dose of 18 mg/kg for the definitive perinatal and postnatal developmental study in rats is acceptable.

RECOMMENDATIONS

1. A final decision as to whether the Sponsor needs to perform an additional 3-month study to support their bridging strategy to the loratadine drug development program must await submission of the histopathology and PK/TK data from the current 3-month study under review. This information was conveyed to the Sponsor by the Project Manager on 12/10/98.
2. The proposed oral high dose of 18 mg/kg for the definitive perinatal and postnatal developmental study in rats is acceptable.

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND 55,364

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/A. Trontell
HFD-570/G. Trout
HFD-570/T.J. McGovern

HFD-570 : DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review #2

IND No. 55,364	Serial No. 007	Submission Date: 08 JUL 98
	009	29 JUL 98
	010	30 JUL 98
	019	18 SEP 98
	023	19 OCT 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 27 OCT 98

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

Sponsor: Schering-Plough Corporation

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

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Route of Administration: Oral (tablet)

Proposed Clinical Protocols:

Objective: Phase III, examining clinical efficacy and safety of SCH 34117

Dose: 5 and 7.5 mg in each proposed study

Frequency: Once per day

Duration of clinical studies: Two 2-week studies and one 4-week study

Patient population: Patients with seasonal allergic rhinitis

Previous Clinical Experience: Phase I, rising single-dose study (2.5-20 mg) in healthy male volunteers. Phase II, dose finding study (2.5-20 mg; two weeks) in patients with seasonal allergic rhinitis.

Previous Review(s), Date(s) and Reviewer(s):

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
Original Review	March 9, 1998	McGovern	May 22, 1998

The submission of Serial No. 023 states that the Briefing Document (Serial No. 007) for a meeting with the sponsor (8/7/98) serves as a summary for the 28-day studies in rats and monkeys submitted as Serial No. 009, since submission No. 009 did not include a summary of results and conclusions. The preclinical studies are in support of the proposed 28-day clinical study included

in the submission labeled Serial No. 010. Submission 019 states that toxicology data submitted on July 2 and 16, 1998 (Serial Nos. 007 and 008, respectively) are considered adequate to support initiation of Clinical Study C98-225, the 28-day study in seasonal allergic rhinitis patients. These serial numbers did not correspond to those received by this reviewer and it is assumed that the sponsor is referring to Serial Nos. 007 and 009 submitted on July 8 and 29, 1998, respectively. Submission 023 adequately addressed the Division's concerns.

The following table summarizes the studies submitted in these submissions:

Preclinical Studies Submitted and Reviewed in this IND:

Study	Serial No.	Report #	Volume
Multiple Dose Toxicology:			
FDA Briefing Document	007		
4-week, oral (gavage) toxicity, rats	009	SN 98088	1
4-week, oral (gavage) toxicity, monkeys	009	SN 98089	1

Studies Not Reviewed in this IND: None.

Studies Previously Reviewed: None

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

MULTIPLE-DOSE TOXICITY:

Rat, 28-day Oral Toxicity

██████████ No.: N003134D Study No.: SN 98088 Volume: 1

Study Dates: Starting date 4/6/98; report issued 7/29/98
Testing Lab: ██████████
Test Article: SCH 34117 (Batch 97-37114-X-03-RA; purity=██████████) in 0.4% methyl-cellulose; Loratadine (Batch MI-A-00851; purity=1 ██████████)
Concentration: 0.6-24 mg SCH 34117/ml; 24 mg loratadine/ml
Dose Volume: 5 ml/kg/day
GLP: The study was an unaudited report.
QA report: No.

Methods: ██████████:CD[®] (SD) BR VAF/Plus[®] rats (5-7 weeks old; males: 100-325 g; females: 80-300 g) were assigned to the following treatment groups:

Dose (mg/kg/day):	0	3	30	60	120	120 mg loratadine/kg/day
No./sex toxicity study	10	10	10	10	10	10

Rats received daily oral doses of vehicle, test drug or comparative dose of loratadine (equal to the high dose of SCH 34117 on a mg/kg basis) for 28 days. The following observations were made:

Clinical observation . . . twice daily
 Body weight weekly beginning Week -1

Food consumption weekly
Water consumption . . . not assessed
Ophthalmoscopy prestudy and during Week 4
EKG not performed
Hematology Day 29
Clinical chemistry Day 29
Urinalysis Day 29
Enzyme induction not assessed
Organ weights at sacrifice; (for specific organs see Addendum, page 14)
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. Organs identified as target organs in the high-dose group also processed and evaluated in all other groups (for specific tissues/organs see Addendum, page 14).
Toxicokinetics Day 1 and during Week 3; samples collected 2 rats/sex/group (test and comparative article groups only)

Results: Results are summarized in tables 1-6.

Mortality: Mortality was not directly addressed in the submitted summary report, although an included protocol change stated that PK sampling in high-dose females during Week 3 was canceled due to excessive mortality of high-dose females during the Day 1 blood collection. Summary data tables for unscheduled deaths included 3 high-dose males and 1 low-dose and lower mid-dose, 3 upper mid-dose, 8 high-dose and 4 loratadine-treated females. In contrast, the submitted briefing document (Serial No. 007) contains a summary data table which provides different numbers (Table 1). The briefing document states that deaths/moribund sacrifices in the 3-60 mg/kg groups occurred on days on which rats were bled for plasma analyses and are not treatment-related. All male animals which died, with the exception of HD males, did so on Day 1 following bleeding. Similarly, all females which died, with the exception of HD females, did so on Day 15 following bleeding. Control animals were not bled and, thus, were not subjected to similar stress. Thus, it is arguable that deaths in the low to upper-mid-dose groups are related to bleeding procedures rather than drug treatment, especially since no mortality was observed in a previous 14-day study at doses up to 60 mg/kg/day. Deaths at 120 mg SCH 34117/kg in the current study, however, appear to be directly related to drug administration since the incidence was increased and deaths did not occur on days of bleeding.

Clinical Observations: Clinical signs with potential treatment-relatedness include enlarged feces, few feces, no feces, salivation, hunched posture, thin appearance, labored and rapid respiration, respiratory distress/respiratory sounds-rales, paleness, and wetness in urogenital region (Table 1). These findings were observed primarily at doses greater than or equal to 30 mg/kg and are thought to be associated with the anticholinergic properties of the test drug.

Body Weight: At Day 29, body weight gain of SCH 34117-treated males was reduced 18 and 34% at the upper-mid and high dose, respectively, and loratadine-treated males were reduced 19% (Table 1). High-dose males first showed significant reduction at Day 8. Similarly, body

weight loss (31g) compared to controls (increase of 55g) was first noted on Day 8 in high-dose females. Loratadine-treated females displayed a 32% reduction in body weight gain.

Food Intake: Reduced food consumption at Day 29 was observed in HD animals (Table 1). A decrease was first reported at Day 8 with the greatest reduction observed at Day 15 in females (25-34% in males; 39-74% in females). Consumption was also reduced in loratadine-treated females beginning at Day 8 (15-29%), although males showed significant reductions only at Days 8 and 22 (9 and 7%, respectively).

Table 1. Clinical observations in rats administered SCH 34117 or loratadine.

Dose (mg /kg/d)	Males						Females					
	0	3	30	60	120	Lorat.	0	3	30	60	120	Lorat.
Mortality*	0	2	2	2	5	2	0	1	1	3	8	4
Clin. Observations												
Enlarged feces			10	10	10	10			10	10	8	9
Few feces					10	1	1	1	10	10		9
No feces					1				1	2		
Alopecia					1							
Salivation			1		4				1	1		
Hunched posture					10						1	
Pale					3		1				9	
Rough coat					1						4	
Thin					8		1		1	10		1
Labored respiration				1	2			1		3		2
Rapid respiration		2	1	2	1					1		
Resp. distress/sounds					4					1		1
Eyes/ears discharge										2		
Nasal discharge										1		1
Urogenital region - wet										6		
Body Weight Gain												
%Δ vs control group		↓6	↓4	↓18	↓34	↓19		↑3	↓20	↓15	↓31**	↓32
Food Consump. (g/day)												
%Δ vs control group		no Δ	↑6	↓4	↓34	↓1		↓2	↓6	↓9	↓39	↓20

* Control animals not bled for plasma analysis. Males: n = 12; females: n = 10.

** Body weight loss in grams.

Shaded areas indicate a significant difference from vehicle controls.

Ophthalmoscopy: No treatment-related observations were reported.

Hematology: Slight increases in white blood cell and erythrocyte counts, hemoglobin and hematocrit and platelets (high-dose) were observed in treated males (Table 2). Similar changes were noted in females, however, white blood cell counts were reduced considerably in high-dose females. Reduced eosinophil levels in high-dose males and females (53 and 87%, respectively) and lymphocyte numbers in high-dose females (87%) were noted. Loratadine-treated animals were comparable to mid-dose SCH 34117 animals, demonstrating slight increases in erythrocyte counts, hemoglobin and hematocrit. Besides the changes in lymphocyte and eosinophil

%Δ vs control group	↓5	↑10	↓32	↑6	↓2	↓14	↓44	↓53	↓14	↓44
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Shaded areas indicate a significant difference from vehicle controls.

Organ Weights: SCH 34117-treated males exhibited decreases in heart, thymus and prostate weight (Table 3). In addition, lung and liver weights were increased. Females showed similar changes in heart and thymus weights, and also demonstrated slight increases in kidney and decreases in spleen and ovary weights. Brain weight was slightly decreased (6-11%) in high-dose animals. Loratadine-treated animals also exhibited significant alterations (usually comparable to animals administered 60 mg/kg SCH 34117) in adrenal gland and spleen weights (males only), heart (females only), and liver and lung weights. Generally, similar changes were observed in "relative to body weight" and "relative to brain weight" organ weights.

Table 3. Absolute organ weight changes following SCH 34117 administration in rats.

Dose (mg/kg/d)	Males					Females				
	3	30	60	120	Lorat.	3	30	60	120	Lorat.
Abs. Organ weight										
Adrenal gland										
%Δ vs control group	↓8	↓11	↓17	↓4	↓22	↓10	↓11	↓2	↓1	↓5
Brain										
%Δ vs control group	↓2	↓1	no Δ	↓6	↓3	↓3	↓1	↓5	↓11	↓3
Heart										
%Δ vs control group	↓2	↓4	↓7	↓18	↓11	↑1	↓7	↓2	↓20	↓11
Kidney										
%Δ vs control group	↓3	no Δ	↑2	↑4	↓7	no Δ	no Δ	↑9	↑21	↑2
Liver										
%Δ vs control group	↓3	↑21	↑26	↑56	↑28	↓8	↓5	↑12	no Δ	↑31
Lung										
%Δ vs control group	↑4	↑25	↑38	↑34	↑36	↑16	↑29	↑72	↑17	↑70
Spleen										
%Δ vs control group	↓2	↓12	↓21	↓15	↓26	↓23	↓28	↓34	↓59	↓26
Thymus										
%Δ vs control group	↑4	↓14	↓17	↓29	↓16	↑7	↓4	↓4	↓60	↓5
Prostate										
%Δ vs control group	↓1	↓9	↓7	↓19	↓5					
Ovary										
%Δ vs control group						↓7	↑9	↑5	↓40	↑2

Gross Pathology: Following scheduled sacrifice, gross alterations included an impacted colon and deformed liver in a high-dose female, and an enlarged seminal vesicle in a high-dose male (Table 4). Following unscheduled deaths, dilatation was noted in numerous organs of a high-dose female and male. Additional observations at the high dose included lung discoloration and enlarged mandibular lymph nodes.

Table 4. Gross changes following SCH 34117 administration in rats.

Dose (mg/kg/d)	Males						Females					
	0	3	30	60	120	Lorat.	0	3	30	60	120	Lorat.
Gross alterations												
Scheduled Sacr. n =	10	10	10	10	7	10	10	9	9	7	2	6
Colon - impacted	0	0	0	0	0	0	0	0	0	0	1	0
Liver - deformity	0	0	0	0	0	0	0	0	0	0	1	0
Seminal ves. - enlarged	0	0	0	0	1	0						
Unscheduled Deaths n =	0	0	0	0	3	0	0	1	1	3	8	4
Cecum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Duodenum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Ileum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Intestines - dilatation	0	0	0	0	1	0	0	0	0	0	0	0
Jejunum - dilatation	0	0	0	0	0	0	0	0	0	0	1	0
Lung - discoloration	0	0	0	0	0	0	0	0	0	0	2	0
LN-mandib - enlarged	0	0	0	0	1	0	0	0	0	0	2	0
Stomach - dilatation	0	0	0	0	1	0	0	0	0	0	0	0

Histopathology: Assessment of histopathological findings in animals following the final sacrifice demonstrated alterations, many indicative of systemic phospholipidosis, in numerous organs (Table 5). These findings were observed primarily at the upper-mid and high dose, although centrilobular hepatic hypertrophy and vacuolation were noted at 30 mg/kg SCH 34117 in males. Similar findings were observed in animals following unscheduled sacrifice. Additional observations in this group included villous atrophy of the ileum (1 of 8 HD females), mammary gland hyperplasia (1 of 8 HD females), inflammation of the esophageal muscularis (1 of 3 HD males, 2 of 8 HD females), cortical tubular necrosis in 1 of 3 HD males and 5 of 8 HD females), alveolar proteinosis in the lungs (1 of 3 UMD and 2 of 8 HD females), necrosis of pancreatic acini (1 of 8 HD females), and congestion (1 of 3 HD males) and lymphoid depletion (7 of 8 HD females) of the thymus. Findings in animals administered loratadine did not correlate with those of SCH 34117-administered animals in all cases and appeared to be less toxic than SCH 34117 at equivalent doses.

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Table 5. Histopathological changes following final sacrifice of rats.

Dose (mg/kg/d)	Males						Females					
	0	3	30	60	120	Lorat.	0	3	30	60	120	Lorat.
Histology-final sacrifice												
Harderian gland n =	10	0	0	0	7	10	10	0	0	0	2	6
inflammation	0	0	0	0	1	0	0	0	0	0	0	1
Eye - retinal folds/cysts	0	0	0	0	1	0	0	0	0	0	1	0
Heart n =	10	10	10	10	7	10	10	9	9	7	2	6
cardiomyopathy	1	0	1	0	3	0	0	1	0	0	2	1
Kidney												
tub vacuolation (cortex)	1	0	0	2	7	5	0	0	0	0	2	2
hyperplasia, epith-pelvis	0	0	0	0	1	0	0	0	0	0	0	0
inflamm, chronic-pelvis	0	0	0	0	1	0	0	0	0	0	0	0
tub dilatation, (cortex)	0	0	0	0	1	0	0	0	0	0	2	0
Liver												
vacuolation-fine,centrilob	0	0	9	9	6	9	0	1	0	4	2	6
-coarse	0	0	0	1	0	1	0	2	0	0	0	0
centrilob hepat hypertr	0	0	10	10	6	10	0	0	0	4	2	6
kupfer cell hypert/vac	0	0	0	0	1	0	0	0	0	0	2	0
Lung												
alveolar histiocytosis	0	0	0	6	7	0	0	0	0	7	2	6
inflammation, chronic	0	0	0	0	1	0	0	0	0	0	0	0
Lymph node-mesenteric												
vacuolated histiocytes	0	0	0	0	4	0	0	0	0	3	2	1
lymphoid depletion	0	0	0	0	1	0	0	0	0	0	0	0
Lymph node - mandib												
vacuolated histiocytes	0	0	0	0	3	0	0	0	0	3	2	0
Ovary												
vacuolation							0	0	0	0	1	1
atrophy							0	0	0	0	1	0
Pancreas												
vacuolation, acinus	0	0	0	0	0	0	0	0	0	0	1	0
Prostate n =	10	0	0	0	7	10						
inflammation, chronic	0	0	0	0	1	0						
Skeletal Muscle n =	10	10	10	10	7	10						
myofiber denervation	0	0	0	0	4	0	0	0	0	0	2	0
Spleen												
lymphoid depletion	0	0	0	0	5	0	0	0	0	0	2	0
vacuolated histiocytes	0	0	0	0	7	0	0	0	0	6	2	0
hematopoiesis	0	0	0	0	1	0	0	0	0	0	0	0
Thymus												
vacuolated histiocytes	0	0	0	0	4	0	0	0	3	0	2	1
Urinary bladder n =	10	0	0	0	7	10	10	0	0	0	2	6
hyperplasia, epithelium	0	0	0	0	1	0	0	0	0	0	0	0
Uterus n =							10	9	9	7	2	6
↓ myo/endometrium							0	0	0	0	2	0
Vagina n =							10	0	2	1	2	6
epithelial mucification							0	0	0	0	2	1

Toxicokinetics: Plasma analysis information was not provided in the study report (Serial No 009), although a summary data table was provided in the briefing package (Serial No. 007). This

information is summarized in Table 6. Following SCH 34117 administration T_{max} increased with increasing dose from 1-4 hours to 24 hours. Generally C_{max} increased proportionally while AUC increased supra-proportionally. Systemic exposure was 2-3 fold greater in females than in males. Exposure to SCH 34117 following 120 mg/kg loratadine administration was similar to exposure following 60 mg/kg SCH 34117 administration, although the T_{max} was reduced. The similarity in exposure may explain the greater comparability in toxicity of loratadine with 60 mg/kg SCH 34117 than with 120 mg/kg SCH 34117. The sponsor was requested to submit the full data set during a meeting on 8/7/98 (see meeting minutes).

Table 6. Toxicokinetics of SCH 34117 and loratadine in the rat.

Dose (mg/kg/d)	Analyte	Gender	T _{max} (hr)	C _{max} (ng/ml)	AUC _(0-24 hr) (ng.h/ml)
3 (SCH 34117)	SCH 34117	M	4	71.2	506
		F	1	134	1619
30 (SCH 34117)	SCH 34117	M	8	990	17088
		F	8	1780	36664
60 (SCH34117)	SCH 34117	M	8	1653	30447
		F	24	2869	57513
120 (SCH34117)	SCH 34117	M	24	3951	77579
		F	ND	ND	ND
120 (Loratadine)	SCH 34117	M	4	1774	37444
		F	1	2763	52232
	Loratadine	M	1	495	3395
		F	2.5	533	4483

M: males. F: females ND: not determined

The low-dose of 3 mg SCH 34117/kg/day in males and the lower mid-dose of 30 mg/kg/day in females were selected as the NOAELs for this study due to the histopathological findings in the liver and histiocytosis and the presence of vacuolated histiocytes in various organs. Target organs of toxicity included the liver, kidneys, lung, spleen, thymus and female reproductive organs.

Monkey, 28-day Oral (Gavage) Toxicity

Study No.: N003134C Study No.: 98089 Volume: 1

Study Dates: Starting date 3/26/98; report issued 7/29/98
 Testing Lab:
 Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not reported) in 0.4% (w/v) aqueous methylcellulose
 Concentration: 0.6-2.4 mg SCH 34117/ml; 2.4 mg loratadine/ml
 Dose Volume: 5 ml/kg/day
 GLP: This report was unaudited.
 QA report: No.

Methods: Cynomolgus monkeys (approximately 2 years of age; 2-4 kg) were assigned to the following treatment groups:

Dose (mg SCH 34117 /kg/day):	0	3	6	12	12 mg loratadine/kg/day
No./sex	4	4	4	4	4

Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 28 days. The following observations were made:

- Clinical observation . . . twice daily
- Body weight weekly
- Food consumption daily
- Water consumption not assessed
- Ophthalmoscopy once pretest and Week 4
- Veterinary exam. twice pretest and Weeks 2 and 4; includes body temperature, respiratory rate, heart rate, blood pressure and ECG measured 4 hours after dosing to coincide approximately with Tmax.
- Hematology twice pretest and Day 29
- Clinical chemistry twice pretest and Day 29
- Urinalysis twice pretest and Day 29
- Enzyme induction not assessed
- Organ weights at sacrifice; (for specific organs see Addendum, page 14)
- Gross pathology at sacrifice
- Histopathology at sacrifice; organs/tissues from vehicle control, comparative control and high-dose SCH 34117, monkeys dying prior to scheduled necropsy and all gross lesions, organs in all groups identified as target organs from high-dose group (for specific tissues/organs see Addendum, page 14).
- Toxicokinetics Day 1 and during Week 3; samples collected at 1.5, 2.5, 4, 8, 12 and 24 hours post-dose; measured for SCH 34117 and loratadine (loratadine-dosed animals only) using gas chromatography (GC).

Results: Results are summarized in tables 7-9.

Mortality: None.

Clinical Observations: No treatment-related effects were observed other than diarrhea in one high-dose male and female monkey.

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.

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

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: No significant treatment-related effects were observed. However, the 4- and 24-hour urine volume in treated males tended to be reduced, although these findings were not statistically significant (Table 7).

Table 7. Clinical findings in monkeys administered SCH 34117.

Dose (mg /kg/d)	Males				Females			
	3	6	12	Lorat.	3	6	12	Lorat.
Urinalysis								
4-hr volume (Day 28)								
%Δ vs control group	↓42	↓36	↓48	↓42	↓39	↓18	↑32	↓30
24-hr volume (Day 29)								
%Δ vs control group	↓62	↓26	↓59	↓76	↓18	↓18	↑46	↓25

Organ Weights: No toxicologically significant treatment-related effects were observed.

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

Histopathology: The sponsor reported that preliminary evaluation of histopathology data indicate that there are no significant treatment-related findings. However, c-cell hyperplasia in the thyroid of one high-dose male and mineralization of the ovary in three high-dose females were noted (Table 8). Animals from the lower-dose groups were not examined except for one low-dose female which did not develop mineralization in the ovary. A previous 14-day study demonstrated ovarian mineralization in 2 of 3 rats administered 6.5 mg/kg; c-cell hyperplasia was not observed at 14 days. Thus, the uncertain treatment-relatedness of these findings suggest that the sponsor should examine the thyroid and ovary samples from the lower dose groups. Additionally, inflammation and infiltration of lymphoid cells were noted in various tissues, although the dose-dependency of these findings is unclear, especially when data from males and females are combined. Similar findings were observed at 14 days. Generally, findings in the loratadine-treated group were similar to those of the high-dose SCH 34117 group including the finding in the ovary but not the thyroid.

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Table 8. Histopathological changes after 28-day administration in monkey.

Dose (mg/kg/d)	Males					Females				
	0	3	6	12	Lorat.	0	3	6	12	Lorat.
Kidney n =	4	0	0	4	4	4	0	0	4	4
-infiltrating cell,lymphoid	1	0	0	3	3	3	0	0	3	4
Salivary gland										
-infiltrating cell,lymphoid	0	0	0	2	2	4	0	0	4	4
Skeletal muscle										
- inflammation - chronic	1	0	0	2	1	0	0	0	0	2
Stomach										
-inflammation - chronic	0	0	0	0	0	0	0	0	1	0
Thyroid gland										
- hyperplasia, c-cell	0	0	0	1	0	0	0	0	0	0
Ovary n =						4	1	0	4	4
- mineralization						0	0	0	3	3

Toxicokinetics: Plasma analysis information was not provided in the study report (Serial No 009), although a summary data table was provided in the briefing package (Serial No. 007). This information is summarized in Table 9. Following SCH 34117 administration T_{max} was 1.5 to 2.5 hours, increasing to 4 hours at the high dose. C_{max} and AUC increased proportionally from the low to high dose on Day 1, although the mid-dose produced exposures that were lower than would be expected, and increased sub-proportionally on Day 14. Exposure to SCH 34117 following 12 mg loratadine/kg administration was similar to exposure following 6 mg SCH 34117/kg administration on Day 1 but slightly greater than on Day 14. T_{max} was similar (2.5 hours) to that of administered SCH 34117. Drug accumulation was apparent regardless of administration form. Systemic exposure was 71-75% greater on Day 14 than on Day 1 at the two lower doses of SCH 34117 and 19% greater at the high dose while exposure to SCH 34117 following loratadine administration was 2.8-fold greater on Day 14 than on Day 1. The sponsor was requested to submit the full data set during a meeting on 8/7/98 (see meeting minutes).

Table 9. Toxicokinetics of SCH 34117 and loratadine in the monkey.

Dose (mg/kg/d)	Analyte	Day 1			Day 14		
		T _{max} (hr)	C _{max} (ng/ml)	AUC _(0-24 hr) (ng.h/ml)	T _{max} (hr)	C _{max} (ng/ml)	AUC _(0-24 hr) (ng.h/ml)
3 (SCH 34117)	SCH 34117	2.5	189	1836	2.5	252	3153
6 (SCH 34117)	SCH 34117	2.5	232	2572	1.5	369	4506
12 (SCH 34117)	SCH 34117	4	870	8728	4	768	10388
12 (Loratadine)	SCH 34117	2.5	210	2218	2.5	458	6217

The NOAEL in males is at least 6 mg SCH 34117/kg/day due to thyroid hyperplasia. A NOAEL in females could not be determined due to the presence of mineralization in the ovaries of high-dose animals which was not assessed in low- or mid-dose animals. A final determination of the NOAELs is pending the submission of histopathology data for the thyroid and the ovary from the low- and mid-dose groups. Target organs of toxicity may include the thymus and the ovary.

Summary of Toxicology

Subacute, oral (gavage) studies were performed for 28 days in rats (3, 30, 60 and 120 mg/kg SCH 34117 and 120 mg/kg loratadine) and monkeys (3, 6 and 12 mg/kg SCH 34117 and 12 mg/kg loratadine). In rats, treatment-related mortality was observed in the high-dose groups. The primary target organs of toxicity were the liver, kidneys, lung, spleen, thymus and the female reproductive organs, although systemic phospholipidosis (vacuolation, histiocytosis) was observed in numerous organs, primarily at the upper-mid and high dose. Observed toxicities included increased lung, liver and kidney (female only) weights and decreased spleen, thymus and ovary weights, changes associated with centrilobular hepatic hypertrophy and vacuolation, cortical tubular necrosis, alveolar proteinosis (females), and congestion and lymphoid depletion of the thymus. Other histological findings included atrophy of the ileum, mammary gland hyperplasia, and pancreatic acini necrosis (one high-dose female). Other findings included clinical signs (enlarged, few or no feces, salivation, hunched posture, thin appearance, labored/rapid respiration, respiratory distress/respiratory sounds-rales, paleness, and wetness in the urogenital region, reduced body weight and food consumption), and gross changes (impacted colon, a deformed liver in a high-dose female, an enlarged seminal vesicle in a high-dose male, lung discoloration, enlarged mandibular lymph nodes and dilatation of numerous organs of one high-dose female and male). Findings in loratadine-treated animals were more comparable with animals administered 60 mg SCH 34117/kg than with 120 mg/kg SCH 34117, due likely to comparable systemic SCH 34117 exposures observed following administration. NOAELs of 3 mg/kg for males and 30 mg/kg for females were selected.

In the monkey, potential target organs of toxicity included the thymus in males and the ovaries. Hyperplasia of the c-cell was reported in one high-dose male and mineralization of the ovary in 3 of 4 high-dose females and active control animals were reported. These findings are currently of unclear significance since, although they were observed in the high-dose group, the low- and mid-dose groups were not assessed. Other findings included consistently reduced urine volume (not statistically significant) and diarrhea in one high-dose male and female. Loratadine-treated animals demonstrated similar toxicity profiles with animals given the high-dose SCH 34117, although the active control animals displayed similar, though slightly greater, exposure to SCH 34117 as the mid-dose SCH 34117 group. Thus, a NOAEL of at least 6 mg/kg was selected for males due to the thyroid finding. A NOAEL in females, however, could not be determined. A final selection of the NOAELs awaits submission of the histopathology data for the thyroid and ovaries from the low- and mid-dose groups.

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Addendum: Histopathology inventory for IND 55,364.

Study No.	P-6526	D18289	SN 98088	P-6527	SN 98089
Duration	14-day	14-day	28-day	14-day	28-day
Species	rat	rat	rat	monkey	monkey
Adrenals	X*		X*	X*	X*
Aorta	X		X	X	X
Bone marrow smear	X		X	X	
Bone (femur)	X		X	X	X
Bone (rib)				X	X
Bone (sternum)	X		X	X	X
Brain:	X*		X*	X*	X*
Cecum	X		X	X	X
Cervix			X		
Colon	X		X	X	X
Duodenum	X		X	X	X
Epididymis	X*		X*	X*	X
Esophagus	X		X	X	X
Eye	X		X	X	X
Fallopian tube					
Fat					
Gall bladder				X	X
Gross lesions	X	X		X	X
Harderian gland	X		X		
Heart	X*		X*	X*	X*
Hypophysis					
Ileum	X		X	X	X
Injection site	NA	NA	NA	NA	NA
Jejunum	X		X	X	X
Kidneys	X*	X*	X*	X*	X*
Lacrimal gland				X	X
Larynx					
Liver	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*
Lymph nodes, cervical					
Lymph nodes (LALN)					
Lymph nodes, mandibular	X		X	X	X
Lymph nodes, mediastinalis					
Lymph nodes, mesenteric	X		X	X	X
Mammary gland	X		X	X	X
Nasal cavity					
Optic nerves			X		
Ovaries	X*		X*	X*	X*
Oviduct					
Pancreas	X	X	X	X	X
Parathyroid	X		X	X	X
Peripheral nerve					
Pharynx					
Pituitary	X*		X*	X*	X*
Prostate	X*		X*	X*	X*
Rectum					
Salivary gland	X*		X*	X*	X*
Sciatic nerve	X		X	X	X
Seminal vesicles	X		X	X	X
Skeletal muscle	X		X	X	X
Skin	X		X	X	X
Spinal cord	X		X	X	X
Spleen	X*		X*	X*	X*
Stomach	X		X	X	X
Testes	X*		X*	X*	X*
Thoracic Limb	X				
Thymus	X*		X*	X*	X*
Thyroid	X*		X*	X*	X*
Tongue	X		X	X	X
Trachea	X		X	X	X
Urinary bladder	X		X	X	X
Uterus	X*		X*	X*	X*
Uterine horn					
Vagina	X		X	X	X

* Organ weight obtained

OVERALL SUMMARY AND EVALUATION

The identified target organs of toxicity in a 14-day oral (gavage) study in rats (15, 60 and 240 mg/kg SCH 34117) were the liver, lung, kidneys and pancreas, although the complete histologic assessment may have identified others. Observed toxicities included increased liver, lung and kidney relative weights associated with histologic findings (vacuolation, necrosis, congestion and foam cells) as well as 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. In the current 28-day oral (gavage) rat study (3, 30, 60 and 120 mg/kg SCH 34117 and 120 mg/kg loratadine), similar findings were observed as well as additional ones which may be the result of the extended dosing duration. Treatment-related mortality was observed in the high-dose groups. The primary target organs of toxicity were the liver, kidneys, lung, spleen, thymus and the female reproductive organs, although systemic phospholipidosis was observed in numerous organs. Pancreatic toxicity was not observed except for acinus vacuolation in one high-dose female. Observed toxicities included increased lung, liver and kidney (female) weights and decreased spleen, thymus and ovary weights; changes associated with centrilobular hepatic hypertrophy and vacuolation, cortical tubular necrosis, alveolar proteinosis (females), and congestion and lymphoid depletion of the thymus. Other findings included clinical signs, gross changes, and, for the most part, slight changes in hematologic and clinical chemistry parameters which demonstrated limited evidence of a dose-response relationship. The observed toxicities of loratadine-treated animals were comparable to animals administered 60 mg/kg SCH 34117 due, probably, to similar systemic exposures of SCH 34117, but generally less than the toxicity in animals administered 120 mg/kg SCH 34117. NOAELs of 3 mg/kg for males and 30 mg/kg for females were selected.

In the monkey, potential target organs of toxicity after 28-days administration (3, 6 and 12 mg/kg SCH 34117 and 12 mg/kg loratadine) included the thymus (hyperplasia of the c-cell) in males and the ovaries (mineralization). These findings are currently of unclear significance since the low- and mid-dose groups were not assessed. Also, neither finding had been reported in previous studies with loratadine. Other findings included reduced urine volume (not statistically significant) and diarrhea in one high-dose male and female. Increased triglyceride levels and urine osmolarity, observed in a 14-day study, were not noted at 28 days (enzyme levels not assessed in the 28 day study). Loratadine-treated animals demonstrated similar toxicity profiles with animals given the high-dose SCH 34117, although the active control animals displayed similar, though slightly greater, exposure to SCH 34117 as the mid-dose SCH 34117 group. Thus, a NOAEL of at least 6 mg/kg was selected for males due to the thyroid finding. A NOAEL in females, however, could not be determined. A final selection of the NOAELs awaits submission of the histopathology data for the thyroid and ovaries from the low- and mid-dose groups.

The sponsor proposed a multiple-dose study to examine the clinical efficacy and safety of SCH 34117 (5 or 7.5 mg/day) for 4 weeks in patients with seasonal allergic rhinitis in addition to two two-week studies at similar doses. The two-week studies are supported by the preclinical studies

submitted in the Original IND Review (dated 5/22/98). The submitted 28-day rat study supports the proposed clinical doses of 5 and 7.5 mg SCH 37114/day since it resulted in NOAELs of 3 and 30 mg/kg/day in males and females, respectively. Similarly, a NOAEL of at least 6 mg/kg in male monkeys was identified in the 28-day study and also supports the proposed clinical doses. However, a NOAEL, could not be determined in the 28-day monkey study due to histological findings at the high dose which were not assessed at the lower doses. The sponsor initiated the proposed clinical trials prior to formal review of the 28-day preclinical studies based upon a preliminary review and results of previous preclinical and clinical studies. However, the sponsor should evaluate and submit for review the pertinent histological data which may be used in determining appropriate doses in future clinical trials.

RECOMMENDATIONS

1. The sponsor should evaluate the thyroid glands and ovaries from low- and mid-dose animals of the 28-day monkey study (Study number 98089) due to the presence of c-cell hyperplasia in the thyroid gland and mineralization in the ovaries of high-dose animals. Also, a clarification of the term "mineralization" should be provided (i.e., type of minerals).
2. In the future, the sponsor should evaluate tissue histopathology from low- and intermediate-dose groups when high-dose groups show an increase in incidence and/or severity compared to control groups.
3. As requested in the meeting of 8/7/98, the sponsor should submit the line listings for the toxicokinetic data from the 28-day rat and monkey studies (Study numbers 98088 and 98089, respectively).

Timothy J. McGovern, Ph.D., Pharmacologist

Draft Comments for Letter to Sponsor:

1.

2.

3.

Original IND 55,364

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/A. Trontell
HFD-570/L. Cobbs
HFD-570/T.J. McGovern

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

IND No. 55,364

Serial No. 000

Submission Date: 09 MAR 98

Reviewer: Timothy J. McGovern, Ph.D.

Review Completed: 22 MAY 98

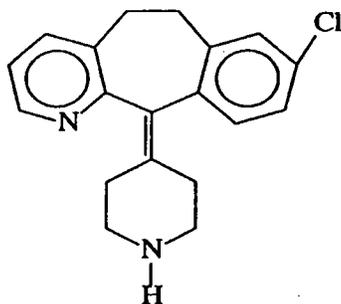
Information to be Conveyed to Sponsor: Yes (✓), No ()

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: C₁₈H₃₁N₄O₃

Related INDs/NDAs/DMFs: NDA 19-658, IND 21,249, IND 41,897, NDA 20-704

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Clinical Formulation: <u>Components</u>	<u>Amount/tablet type (mg)</u>		
	2.5 mg	5 mg	10 mg
SCH 37114	_____		
Dibasic calcium phosphate dihydrate USP	_____		
Cellulose microcrystalline NF11	_____		
Corn starch NF	_____		
Talc USP	_____		
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:

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Preclinical Studies Submitted and Reviewed in this IND:

Study	Report #	Volume
Pharmacology:		
Comparative antihistaminic 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 P-6482, Vol. 1.10), rat (P-6481, Vol. 1.11), cynomolgus monkey (P-6131, Vol. 1.13) and human plasma (P-6738, Vol. 1.14) by gas-liquid chromatography with a nitrogen-phosphorous detector. The assay for Studies P-6482 and P-6481 was validated over the range of 0.2 to 60.0 ng/ml using a 0.5 ml sample. The assay for Study P-6131 was validated over the range of 0.5 to 150 ng/ml using a 0.2 ml sample. The assay for Study P-6738 was validated over the range of 0.1 to 20.0 ng/ml using a 1.0 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 H₁-receptor affinity than the parent drug loratadine, as the two drugs displaced radioligand binding to a cloned H₁ human receptor subtype with IC₅₀ values of 51 and 721 nM, respectively². Both compounds were highly selective and showed little affinity for H₂ or H₃. In isolated guinea pig lung tissue, representative of peripheral H₁ receptors, SCH 34117 again showed greater affinity as IC₅₀s 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 ileum¹. *In vivo*, SCH 34117 also exhibited 2-3 fold greater oral potency over loratadine (doses not provided) in histamine-induced weal and flare reactions¹. 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 antihistaminic 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 M₁-M₃ receptor subtypes, SCH 34117 expressed a high affinity for the M₁ and M₃ receptor subtypes (IC₅₀ of 48 and 125 nM, respectively)¹. Conversely, a weak affinity for the M₂ receptor (IC₅₀ 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 Hartley 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 μ M and value could not be determined.

pA₂ - 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 M₃ receptors, topical-induced mydriasis, and oxotremorine hypothermia (measures of M₂ and M₃ receptor response) and OXO-induced tremor (M₃-mediated) were assessed along with fexofenadine, carebastine, terfenadine, loratadine and ebastine in mice³. Only SCH 34117 inhibited pilocarpine-induced salivation in mice (IC₅₀ = 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 (ED₅₀ = 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 rectifier⁴. 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 μ M; similar results were observed in guinea pig cardiomyocytes. The suppression at 10 μ M (15%) was irreversible upon washout. SCH 34117 had similar effects at doses up to 2.5 μ M (5% suppression) and irreversibly and non-specifically suppressed I_{K1} at 10 μ M. In contrast, the I_{K1} was suppressed by 40% at 1 μ M terfenadine. Loratadine had no significant effect on the delayed rectifier channel (I_{Ks}) until doses > 1 μ M were tested; 25 μ M 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 μ M. 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 assessed⁵. 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 -receptors. 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 μ M) also inhibited a cloned human hKv1.5 current with an K_D of 12.5 μ M, but was less potent than loratadine or terfenadine ($K_D=1.0$ and 0.8 μ M, 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 μ g/ml) at least 5500X greater than plasma levels in man⁶. Although SCH 34117 was not administered directly, the resulting SCH 34117 concentrations (1.46 μ g/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).

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

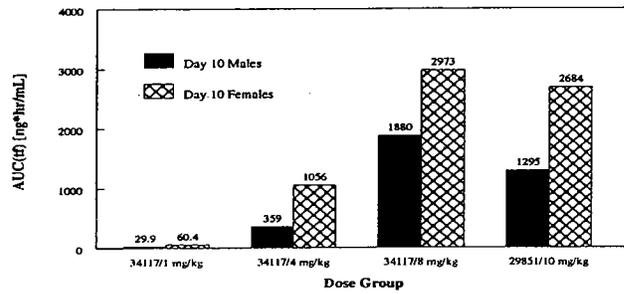
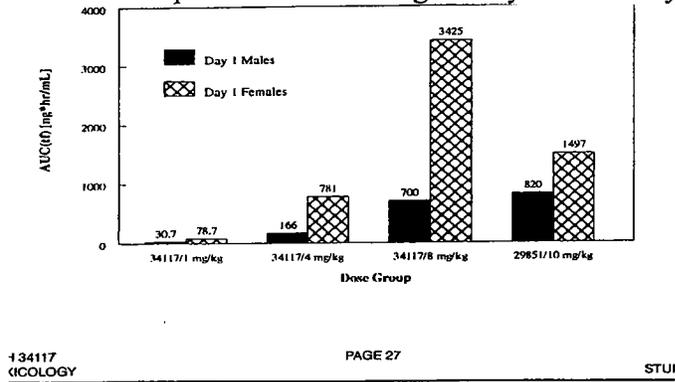


Figure 2. SCH 34117 exposure in monkeys during 14-day oral toxicity study.

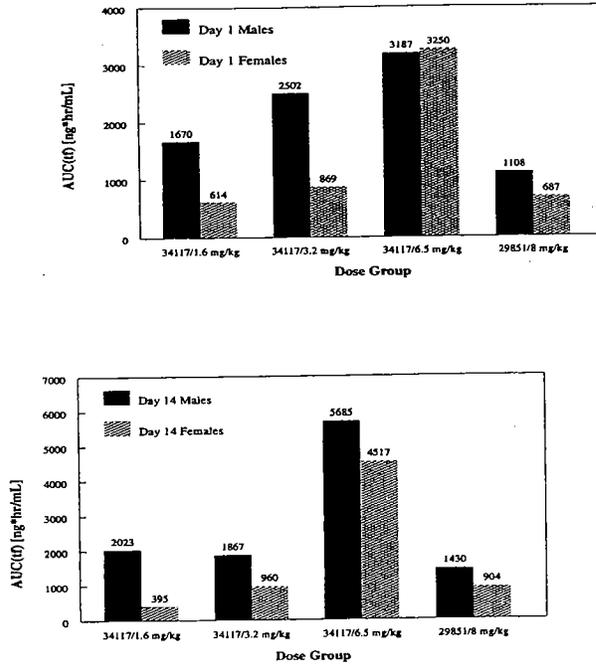


Table 4. Single dose toxicokinetics of SCH 34117 in humans.

SCH 34117 (mg)	t _{1/2} (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 _{1/2} (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 HPLC and mass spectrometer, male rats, mice and a monkey received single doses of ¹⁴C-loratadine, ¹⁴C-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.

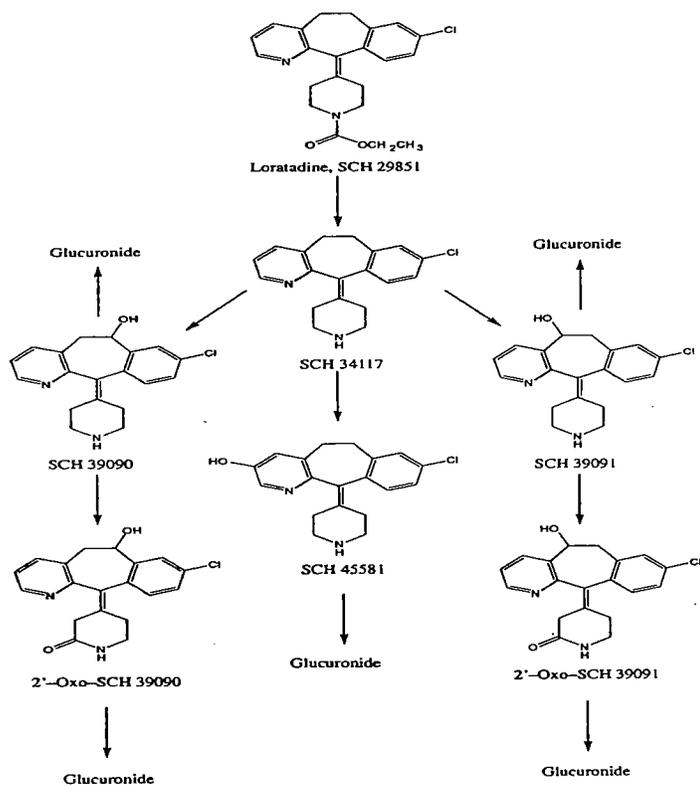


Table 6. Relative abundance of metabolites following oral, single dose administrations.

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.

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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 50 125 250 500	10			M: 353 F: 353	ataxia, convulsions, gasping, hypoactivity, tremors, cool to touch, no feces, pallor, prostration, urogenital staining (M), salivation (1 F); (500 mg/kg)	
		10					
		10					
		10	10	w/in 1 hr			
	IP	P-6772 25 50 125 250 500	10			M: 49 F: 46	hypoactivity (≥ 50), ataxia, convulsions, tremors, prostration, dehydration (≥ 125), gasping (≥ 250), cool to touch (1 each; 50, 250, 500), pallor (1 M; 125), urogenital staining (M; 50 and 125), inguinal swelling (1M; 50)
			10	3M, 4F	Day 2 to 4		
			10	10	2 min to 5 d		
			10	10	w/in 24 h		
			10	10	w/in 24 h		
			10	10	w/in 24 h		
Rats	P-6769 50 125 250 500 2000	10			M: 616 F: 549	cool to touch, hypoactivity, dehydration and urogenital staining (≥ 250), vocalizations, convulsions, tremors, salivation and chromodacryorrhea (2000), scant feces (250 & 500), no feces (250 & 2000), chromorhinorhea (≥ 500), gasping & abdominal distension (1M; 250) BW: Males: ↓ Day 8; ↑ Day 15 (50-500) Females: ↓ Day 8 and 15 (50-500)	
		10					
		10	1M	Day 5			
		10	1M, 1F	24 hr to 2 d			
		10	10	w/in 15 min			
	IP	P-6770 25 50 125 250 500	10			M: 178 F: 68	inguinal swelling (≥ 25), ataxia, cool to touch and hypoactivity (≥ 50), abdominal distension, no/scant feces and urogenital staining (50, 125 & 500), dehydration (50, 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)
			10	3F	5, 9, or 14 d		
			10	3M; 4F	w/in 24 h		
			10	3M; 4F	w/in 24 h		
			10	4M; 5F	15 min - 7 d		
Monkey	P-6808 11.75 23.5 46.9 93.75 125 250	2		None		emesis in males (≥ 23.5) and females (≥ 93.75), diarrhea (1M: 93.75; 1F: 250), Food consumption: ↓ Day 2 (M: 46.9 & 93.75)	
		2					
		2					
		2					
		2					
		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 = █████ 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: █████ :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-pentoxeresorufin 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 a gas liquid chromatographic assay (GLC; LOQ = █████)

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.

Dose (mg /kg/d)	Males					Females				
	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 bilirubin										
%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.

Dose (mg/kg/d)	Males					Females				
	0	1	4	8	Lorat.	0	1	4	8	Lorat.
Enzyme Induction										
PROD (pmol/min/mg mic. prot.)	47		100	133	291	13		17	19	30
EROD (pmol/min/g liver)	1791		2509	2357	2670	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.

Dose (mg/kg/d)	Males					Females				
	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 gas chromatography. 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	$t_{1/2}$ (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.

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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: CD 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).

Dose (mg /kg/d)	Males			Females		
	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.

Dose (mg/kg/d)	Males				Females			
	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.

Dose (mg/kg/d)	Males				Females			
	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 twice 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.

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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	284	264	1	2.35	4.80
	13	257	357	12	2.45	3.43
60	1	417	646	1	2.90	3.63
	13	1046	1207	12	2.23	7.1
240	1	572	911	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 =) 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-pentoxoresorufin 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 a gas liquid chromatographic assay (GLC; LOQ = ████████)

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.

Dose (mg/kg/d)	Males					Females				
	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.

Dose (mg/kg/d)	Males					Females				
	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	24.7	24.1
Enzyme Induction										
PROD (pmol/min/mg mic. prot.)	1.1	0.9	1.3	1.9	2.0	2.5	3.2	3.4	4.5	4.1
EROD (pmol/min/mg mic. prot.)	469	569	540	905	1038	304	433	602	1220	926

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.

Dose (mg/kg/d)	Males				Females			
	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. Infiltr.	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 gas chromatography. 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	$t_{1/2}$ (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.

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Addendum: Histopathology inventory for IND 55,364.

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 =) 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: 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 pre-mating 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 pre-mating dosing period. No stool was observed in one high-dose animal.

Body weight: Pre-mating 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.

<i>Dose (mg/kg)</i>	<i>Males</i>				<i>Females</i>			
	<i>0</i>	<i>6</i>	<i>24</i>	<i>48</i>	<i>0</i>	<i>6</i>	<i>24</i>	<i>48</i>
Body wt gain, prematuring % Δ vs control		↓18	↓11	↓59		↑28	↑34	↓116
Body wt gain, gestation Day 6 % Δ vs control						↓18	↓8	↓54
Clinical observations								
<u>Premating period:</u>								
-reduced stool	0	0	0	5	0	0	2	7
-large fecal pellets	0	0	4	5	0	0	8	5
-chromorrhinorrhea	0	1	0	2	0	0	0	0
<u>Gestation period:</u>								
-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 prematuring 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 (prematuring administration of 9-10 weeks in the case of positive findings); the present dose-ranging study included a 3-week prematuring 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 = █████) 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: █ 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.

<i>Dose (mg/kg)</i>	<i>Females</i>				
	<i>0</i>	<i>3</i>	<i>12</i>	<i>24</i>	<i>48</i>
Maternal body wt gain -dosing period					
% Δ vs control		↓5	↓28	↓52	↓72
Fetal body wt					
% Δ vs control		↓4	↓4	↓9	↓12

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

<i>Dose (mg /kg/day):</i>	<i>0</i>	<i>25</i>	<i>50</i>	<i>100</i>	<i>150</i>	<i>225</i>	<i>300</i>
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

7 days. No unusual clinical signs or necropsy findings were observed. Food consumption was reduced in rabbits dosed with ≥ 100 mg/kg (graded as “ate poorly”) and body weights were suppressed in all rabbits during the dosing period (3-13%). Food consumption in the rabbit given 100 mg/kg returned to normal within a day after dosing was stopped.

Phase II: Based upon the results of Phase I, in which animals dosed with ≥ 150 mg/kg/day died, animals in Phase II were administered 0, 25, 50 or 100 mg/kg/day.

Mortality: Three high-dose females were found dead on Gestation Days 13, 17 and 23, respectively. A fourth had blood in the litter pan on Day 27, aborted on Day 28 and was subsequently sacrificed.

Clinical signs: Clinical signs observed in high-dose rabbits prior to death included lack of stool, soft stool, small fecal pellets and a reduced number of fecal pellets. In the mid-dose group findings included reduced numbers of fecal pellets, abnormally shaped pellets, and soft stool. No unusual clinical signs were noted in the low-dose group except for one female which had a slight amount of blood in the litter pan on Days 26-29 and red vaginal discharge on Day 26.

Body weight: Reduced in 4 high-dose animals that died.

Food Consumption: Reduced in 4 animals that died. Slightly decreased in mid-dose group.

Necropsy: One of the high-dose animals which died had pale tissues, lungs and kidneys, which is not considered an unusual finding in rabbits.

Uterine/ovarian exam and fetal body weight: Drug-related effects on reproduction parameters and fetal body weight were not evident in the low- and mid-dose groups. Data was unavailable for the high-dose group due to maternal mortality.

Fetal gross examination: No SCH 34117-related findings were observed. One control animal exhibited omphalocele.

A NOAEL of 50 mg/kg was identified in this study based upon the observed maternal deaths at the high-dose. Thus, the high-dose in a definitive embryo-fetal development study in rabbits should be between 50 and 100 mg/kg/day, in concurrence with the sponsor’s conclusion.

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Rabbit (oral) Segment II Reproductive Toxicity Study
Report No.: P-6802 *Study No.:* 97116 *Volume:* 1.9

The sponsor submitted only preliminary data tables of body weights, necropsy observations, reproduction data, fetal gross observations and skeletal observations. The following review is based upon the summary provided in the Integrated Toxicology Summary (Volume 1.3).

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 and 97-34117-X-02RA; purity = NA) in 0.4% (w/v) aqueous methylcellulose
Concentration: 7.5-30 mg SCH 34117/ml
Dose Volume: 2 ml/kg/day
GLP: The study was an unaudited report.
QA report: No.

Methods: (NZW) SPF rabbits (females; ~ 5 to 6 months of age) were assigned to the following treatment groups:

Dose (mg /kg/day):	0	15	30	60
No. teratology study	20	20	20	20
No. plasma analysis	3	3	3	3

All rabbits were dosed once daily from Day 7 through Day 19 after mating by gastric intubation. The following observations were made:

Clinical observation: . . . daily
Body weight: Days 0, 7, 10, 13, 16, 19, 22, 25, 28 and 30
Food consumption: . . . gestation days 0-30
Plasma Analysis Days 19/20 (1, 3, 12 and 24 hours)
Necropsy/C-section: . . . Day 30
Uterine/ovarian exam: . number of implantation sites, corpora lutea, fetuses and resorptions
Fetal body weights Day 30
Fetal gross/skeletal exam . at sacrifice

Results:

Mortality: None.

Clinical signs: A change in formed stool was observed in most mid- and high-dose rabbits and some low-dose rabbits.

Body weight: Mean body weight gain in high-dose rabbits was significantly reduced compared to controls over gestation days 10-16 (125%).

Food Consumption: A slight decrease in food consumption was noted in high-dose animals on scattered days throughout the study.

Necropsy: No treatment-related effects.

Uterine/ovarian exam: The mean number of resorptions was increased in the high-dose group.

Plasma analysis: Exposure to SCH 34117 increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg (mean AUCs of 1660, 4087 and 12987 ng.hr/ml at doses of 15, 30 and 60 mg/kg, respectively). Plasma concentrations peaked within 3 hours.

Fetal body weight: No treatment-related effects were observed.

Fetal gross/skeletal examination: No SCH 34117-related findings were observed.

A NOAEL was not identified in this study due to the preliminary and incomplete nature of the submission. The sponsor, however, concluded in this summary that the NOAEL for both maternal and *in utero* effects was 30 mg/kg based upon the higher incidence of resorptions in the high-dose group and that the drug provided no evidence of teratogenic potential under the conditions of this study. The sponsor should submit a complete report of this study.

Summary of Reproductive Toxicology Studies

Pilot Segment I and II studies in rats and a pilot Segment II study in rabbits were submitted by the sponsor. In addition, preliminary data tables for the definitive Segment II study in rabbits were submitted. In the Segment I study, most treatment-related effects in rats orally administered SCH 34117 (6-48 mg/kg), were observed at the high-dose and included one death (female), reduced stool, large fecal pellets, reduced pre-mating body weight gain of males and females and reduced male and female mating indices, although no clear effects on fertility were observed. An increased time to identify positive evidence of mating (143 to 325%) was also noted at the mid- and high-dose. Reproductive effects were limited to the high-dose group and included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal. A NOAEL of 24 mg/kg and a lethal dose of 48 mg/kg were identified for this study. The sponsor should consult ICH guidelines for reproductive toxicology studies when initiating the definitive Segment I study since males were dosed for only 21 days prior to mating in this pilot study. In the pilot Segment II study, female rats were dosed (3-48 mg/kg) once daily by esophageal intubation. Significant findings included a dose-dependent reduction in maternal body weight gain during the dosing period (upper-middle and high-dose animals, 52 and 72%, respectively) and reduced fetal body weights at the high-dose (12.5%). A NOAEL of 12 mg/kg was identified in this study. The oral high-dose in the definitive rat Segment I study should be less than 48 mg/kg and the high-dose in the definitive Segment II study should not exceed 48 mg/kg.

In the pilot Segment II study in rabbits (dosed 25 to 100 mg/kg), three high-dose females were found dead and one was aborted during gestation. Clinical signs included lack of stool, soft stool, small fecal pellets, reduced number of fecal pellets and reduced body weight and food consumption. Effects on reproduction parameters were unavailable for the high-dose group due to maternal mortality and were not evident in the low- and mid-dose groups. In addition, no SCH 34117-related findings were observed during the fetal examination. A NOAEL of 50 mg/kg was identified in this study and the high-dose in a definitive embryo-fetal development study in rabbits should be between 50 and 100 mg/kg/day. Preliminary findings from the definitive Segment II study (15-60 mg/kg) included a change in formed stool in most mid- and high-dose rabbits and some low-dose rabbits and a reduced mean body weight gain in high-dose rabbits (125%). Although an increased number of resorptions occurred in the high-dose group, no changes in fetal body weight or gross/skeletal examinations were observed. Exposure increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg and plasma concentrations peaked within 3 hours. The NOAEL for both maternal and *in utero* effects was 30 mg/kg. The sponsor should submit a complete report of this study when it becomes available.

GENETIC TOXICOLOGY

In vitro Reverse Mutation Assay (Ames Assay)

Report No.: P-6609 Study No.: 97027 Volume: 1.16

Study endpoint: Mutagenicity
Study Dates: Starting date 2/20/97; report issued 9/17/97
Testing Lab: Schering-Plough Research Institute, Lafayette, NJ
Test Article: SCH 34117 (Batch 97-11001-139) diluted in 50% ethanol
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

Methods: SCH 34117 was assayed in 5 Salmonella tester strains and 1 E. coli strains ± metabolic activation by Aroclor 1254-induced rat liver S9 fraction. The following strains and positive controls were used in 2 plate incorporation tests:

Strain	Positive Controls Without S9 (µg/plate)	Positive Controls With S9 (µg/plate)
TA 1535	sodium azide (5)	2-aminoanthracene (2.5)
TA 97a	9-aminoacridine (75)	2-aminoanthracene (2.5)
TA 98	2-Nitrofluorene (5)	2-aminoanthracene (2.5)
TA 100	sodium azide (5)	2-aminoanthracene (2.5)
TA 102	Cumene hydroperoxide (50)	2-aminoanthracene (5)
WP2 uvrA	N-Ethyl-N'-nitro-N-nitrosoguanidine (2)	2-aminoanthracene (20)

SCH 34117 and positive controls were dissolved in 50% ethanol. A dose-ranging assay was performed to determine cytotoxicity (a reduction in revertant colony counts by ~ 30%, inhibition of background bacterial lawn growth and "additional factors based on scientific judgment") after

a 72 hr incubation at 8 half-log concentrations (1.6-5000 µg/plate). Based upon the results of the dose-ranging study, the two mutagenicity assays were conducted at the following concentrations:

Bacterial strain	Phase	EXP 1 Doses (µg/plate)	EXP 2 Doses (µg/plate)
TA 1535	nonactivation	31.3, 62.5, 125, 250, 500	62.5, 125, 250, 500, 1000
TA 97A	nonactivation	3.91, 7.81, 15.6, 31.3, 62.5	3.91, 7.81, 15.6, 31.3, 62.5
TA 98	nonactivation	62.5, 125, 250, 500, 1000	31.3, 62.5, 125, 250, 500
TA 100	nonactivation	15.6, 31.3, 62.5, 125, 250	15.6, 31.3, 62.5, 125, 250
TA 102	nonactivation	15.6, 31.3, 62.5, 125, 250	7.81, 15.6, 31.3, 62.5, 125
WP2uvrA	nonactivation	94, 188, 375, 750, 1500	188, 375, 750, 1000, 1500
TA 1535, WP2uvrA	activation	94, 188, 375, 750, 1500	94, 188, 375, 750, 1500
TA 97A	activation	7.81, 15.6, 31.3, 62.5, 125	3.91, 7.81, 15.6, 31.3, 62.5
TA 98	activation	31.3, 62.5, 125, 250, 500	31.3, 62.5, 125, 250, 500
TA 100, TA 102	activation	31.3, 62.5, 125, 250, 500	15.6, 31.3, 62.5, 125, 250

The experiments were performed using triplicate plates at each concentration incubated for 48 hours ± S9. Tests were valid if overnight bacterial cultures reached a density of 5×10^8 cells/ml, the mean number of revertant colonies/plate was within the range of the historical solvent control values of the same strain and the mean number of revertants/plate in the positive controls was at least three-fold greater than the mean of its concurrent solvent control for TA 1535, and at least two-fold greater than the mean of their respective concurrent controls for *E. coli* and other *Salmonella* strains. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in one of the six tester strains. The magnitude of increase was at least two-fold above the solvent control for strains TA 97A, TA 98, TA 100, TA 102 and WP2uvrA, and three-fold above the solvent control for strain TA 1535. In addition, a dose-response increase of revertant counts in treated plates above that of the solvent control was observed in at least two dose levels, and the increases were reproducible in independent trials.

Results: In the dose-ranging study, significant cytotoxicity was observed without S9 activation at concentrations of ≥ 500 µg/plate for TA 1535, TA 98, TA 100 and WP2uvrA. In strains TA 97A and TA 102, cytotoxicity was observed at concentrations ≥ 50 and 158 µg/plate, respectively. Complete cytotoxicity was observed in all *Salmonella* strains at ≥ 1581 µg/plate and 5000 µg/plate WP2uvrA, respectively. Background lawn growth and microcolonies were markedly reduced in all *Salmonella* strains at 500 µg/plate, and in the WP2uvrA strain at 1581 µg/plate. In the activation phase, cytotoxicity was observed in the TA 97A strain at ≥ 158 µg/plate, ≥ 500 µg/plate for strains TA 100, TA 98 and TA 102, and ≥ 1581 µg/plate for TA 1535 and WP2uvrA. Marked cytotoxicity was observed in TA 102 at 500 µg/plate, and in all strains at 1581 µg/plate. Complete cytotoxicity was observed at 5000 µg/plate in all strains.

In the first mutagenicity trial, SCH 34117 did not increase revertant colony counts, ± S9 activation. Positive controls significantly increased the number of revertant colonies. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 62.5 µg/plate for TA 97a, 125 µg/plate and above for TA 102, 250 µg/plate for TA 100, 500 µg/plate and above for TA 98 and at 1500 µg/plate for WP2uvrA. Slight cytotoxicity to the background lawn was observed at 250 µg/plate for TA 102, and marked cytotoxicity to background lawn and microcolonies were

noted at 500 µg/plate for TA 1535, 500 µg/plate and above for TA 98 and at 1500 µg/plate for WP2uvrA. In the activation phase, cytotoxicity to revertant colonies was observed at 62.5 µg/plate for TA 97a, 125 µg/plate and above for TA 102, 250 µg/plate and above for TA 100, 500 µg/plate for TA 98, 750 µg/plate and above for WP2uvrA and 1500 µg/plate for TA 1535. Slight cytotoxicity to the background lawn was observed at 250 µg/plate for TA 102, and at 1500 µg/plate for WP2uvrA. Marked cytotoxicity to background lawn and microcolonies were noted at 500 µg/plate for TA 100 and 102, and at 1500 µg/plate for TA 1535. Similar results were observed in the second mutation trial.

Thus, SCH 34117, up to 1500 µg/plate, was negative in the bacterial mutation test (Ames assay) using plate incorporation, in concurrence with the sponsor's conclusion.

Chromosome Aberration Study in Human Peripheral Lymphocytes

Report No.: P-6692 *Study No.:* 97028 *Volume:* 1.16

Study endpoint: Clastogenicity
Study Dates: Starting date 2/26/97; report issued 9/18/97
Testing Lab: _____
Test Article: SCH 34117 (Batch 97-11001-139) diluted in 50% ethanol
GLP: The study was accompanied by a signed GLP statement.
QA report: Yes.

Methods: A series of chromosome aberration assays were performed ± metabolic activation (S9 fraction from Aroclor 1254-treated rats) using whole blood from two healthy donors, one male and one female. Duplicate cultures were exposed to either negative controls, solvent control, doses of SCH 34117 (adjusted in duplicate assays for toxicity) or doses of positive control. Assays were conducted with 24 and 48 hour treatment times without metabolic activation (male: 6.25-1500 µg/ml; female: 6.25-125 µg/ml) followed by 27 and 51 hour harvests, respectively. In addition, assays with a 3 hour treatment time ± metabolic activation (male: 6.25-1500 µg/ml; female: 12.5-200 µg/ml) followed by ~ 24 and 48 hour harvests were performed. The test drug was dissolved in 50% ethanol, while the positive controls, mitomycin C (for the nonactivation assays) and cyclophosphamide (for the activation assays) were dissolved in sterile deionized water. The mitotic index was assessed by analyzing the number of mitotic cells in 1000 cells/culture. Cultures with a mitotic index < 40% of the solvent control were not scored for chromosome aberrations. One hundred cells, if possible, were analyzed from each duplicate culture for chromosome aberrations at the four highest dose levels of SCH 34117 (3 in the assay with metabolic activation, ~ 3 hr treatment and 24 hr harvest, donor 1), the negative control, solvent control and at one dose level of the positive control. At least 25 cells were analyzed from those cultures with greater than 25% of cells with one or more aberrations. In addition, the percentages of polyploidy and endoreduplication from at least one hundred cells from each duplicate culture were analyzed. A response was considered positive if the test article induced statistically significant increases in the number of cells with aberrations over those of the solvent controls at one or more concentrations in two donors and the increases showed a positive dose-

response, or if the test article induced statistically significant increases in the number of cells with chromosome aberrations in at least two consecutive concentrations in two donors.

Results: Osmolality of the test sample was comparable to that of the solvent control. The pH of the test sample was 8.5 versus 8.0 for the solvent control. In all assays a precipitate was formed at doses of 500 to 1500 µg/ml. Lysis was also observed after dosing with 1000 and 1500 µg/ml; and at the time of washing the cell cultures at 125-1500 µg/ml.

Under the conditions tested in this assay, SCH 34117 did not induce chromosomal aberrations, polyploidy or endoreduplication in cell cultures with or without metabolic activation at doses up to 15 µg/ml and 10 µg/ml (male and female donor, respectively: 24 hour treatment/27 hour harvest without metabolic activation), 25 and 10 µg/ml (male and female donor, respectively: 48 hour treatment/51 hour harvest without metabolic activation), 125 and 100 µg/ml (male and female donor, respectively: 3 hour treatment/24 hour harvest with metabolic activation), 125 and 130 µg/ml (male and female donor, respectively: 3 hour treatment/48 hour harvest with metabolic activation) and 90 and 50 µg/ml (male and female donor, respectively: 3 hour treatment/24 hour harvest without metabolic activation). Doses above those cited above induced levels of cytotoxicity which lead to mitotic indices < 40% and these cultures were not assessed for chromosomal aberrations. Increased incidences of chromosome aberrations were observed in cultures dose with the positive control agents, cyclophosphamide and mitomycin C. Negative and solvent controls were within historical ranges.

SCH 34117 is considered negative for inducing chromosome aberrations in cultured whole blood human lymphocytes from a male and female donor in the presence or absence of an exogenous metabolic activation system at doses up to 125 µg/ml in the male donor and 130 µg/ml in the female donor.

OVERALL SUMMARY AND EVALUATION

Pharmacology: SCH 34117 displayed a 14-fold greater affinity for the H₁-receptor than loratadine and was more up to 20-fold more potent than loratadine in its antihistaminic activity in guinea pigs. The potency of the two compounds was comparable in inhibiting histamine-induced airway effects in monkeys. SCH 34117 also showed a similar affinity for M₁ and M₃-receptors, but not for M₂-receptors. In comparison, 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 (IC₅₀ = 10.8 mg/kg po and 3.2 mg/kg sc; loratadine significantly inhibited salivation (24%) only at highest dose of 30 mg/kg po). SCH 34117 was 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 (ED₅₀ = 2.7 mg/kg), but did not affect oxotremorine hypothermia and

OXO-induced tremor. Both SCH 34117 and loratadine displayed limited potency 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: In a study cited by the sponsor and included in the IND package, loratadine (30 and 100 mg/kg, iv) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 μg/ml). Resulting SCH 34117 concentrations (1.46 μg/ml) were 370X greater than its C_{max} in man after a single oral dose of 10 mg loratadine. However, terfenadine, quinidine and diphenhydramine induced significant cardiovascular and ECG effects. This study, in combination with in vitro assessments of rat and guinea pig cardiac K⁺ channels and the 14-day oral toxicity study in monkeys, suggests that SCH 34117 does not possess significant cardiovascular activity. The acting Medical Officer, Dr. Peter Honig, was consulted and agreed that no further preclinical assessment of cardiovascular effects is necessary.

Pharmacokinetics: 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.

Acute Toxicity: 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 and respiratory system in rats and mice and the gastrointestinal system in monkeys.

Subacute Toxicity: 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 a complete histologic assessment may have identified others. 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. 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. The significance of the findings could not be determined since the sponsor did not evaluate tissues from animals administered lower doses and since small numbers of animals were used. Other findings 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.

Reproductive Toxicology: In a Segment I study in rats (6-48 mg/kg SCH 34117, oral) most treatment-related effects were observed at the high-dose and included one death (female), reduced stool, large fecal pellets, reduced pre-mating body weight gain and male and female mating indices, although no clear effects on fertility were observed. Time to identify positive evidence of mating was also increased (143 to 325%) at the mid- and high-dose. Reproductive effects included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal at the high-dose. A NOAEL of 24 mg/kg and a lethal dose of 48 mg/kg were identified for this study. The sponsor should consult ICH guidelines for reproductive toxicology studies when initiating the definitive Segment I study, as males were dosed for only 21 days prior to mating in this pilot study. In a pilot Segment II study (3-48 mg/kg), significant findings in female rats included reduced maternal body weight gain during the dosing period (upper-middle and high-dose animals) and fetal body weights at the high-dose. A NOAEL of 12 mg/kg was identified in this study. The high-dose in the definitive rat Segment I and Segment II studies should be less than 48 mg/kg and should not exceed 48 mg/kg, respectively.

In the pilot Segment II study in rabbits (25 to 100 mg/kg), clinical signs included deaths, lack of stool, soft stool, small fecal pellets, reduced number of fecal pellets and reduced body weight and food consumption. Effects on reproduction parameters, unavailable for the high-dose group due to maternal mortality, were not evident in the low- and mid-dose groups and no findings were observed during the fetal examination. A NOAEL of 50 mg/kg was identified in this study and the high-dose in a definitive embryo-fetal development study should be between 50 and 100 mg/kg/day. Preliminary findings from the definitive Segment II study (15-60 mg/kg) included a

change in formed stool at the mid- and high-dose and in some low-dose rabbits, as well as reduced mean body weight gain at the high-dose. Although an increased number of resorptions occurred in the high-dose group, no changes in fetal body weight or gross/skeletal examinations were observed. Exposure increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg and plasma concentrations peaked within 3 hours. A preliminary NOAEL of 30 mg/kg was identified and the sponsor should submit a complete report of this study.

Genotoxicity: SCH 34117 was negative in the bacterial mutation test (Ames assay) using the plate incorporation method at concentrations up to 1500 µg/plate. SCH 34117 was also negative in a chromosome aberration assay in cultured whole blood human lymphocytes in the presence or absence of an exogenous metabolic activation system at doses up to 125 µg/ml in the male donor and 130 µg/ml in the female donor. Significant cytotoxicity occurred at doses higher than the maximum reported.

The sponsor has proposed a Phase II, multiple-dose study to examine the clinical efficacy and safety of SCH 34117 (2.5-20 mg/day) for 2 weeks in patients with seasonal allergic rhinitis. The preclinical 14-day studies in rats and monkeys resulted in NOAELs of 8 and 6.5 mg/kg/day, respectively, although both studies resulted in numerous histological findings of slightly greater incidence at the high dose compared to control groups. A definitive assessment of these findings could not be determined since the sponsor did not evaluate the tissues of the low- and intermediate-dose groups. However, these findings are not of great concern since they were of generally low severity and did not fit within the general toxicity profile of SCH 34117 and its parent compound loratadine. Furthermore, the expected exposure levels in clinical trials at the proposed maximum dose of 20 mg/day should be considerably less than those reported in the preclinical studies. A previously completed Phase I single-dose study (2.5-20 mg) in healthy male volunteers resulted in a mean AUC of 158 ng.h/ml at the high-dose. This exposure level could reasonably be expected to rise to 300 ng.h/ml in a 14-day study, assuming drug accumulation observed in clinical trials with loratadine. An exposure of this level is still considerably below those observed in rats and monkeys at the doses in which the questionable histological findings were observed. Thus, the proposed clinical trial is considered to be reasonably safe to proceed.

RECOMMENDATIONS

1. The clinical trial may proceed as proposed (up to 20 mg SCH 34117/day for 14 days).
2. In the future, the sponsor should evaluate tissue histopathology from low- and intermediate-dose groups when high-dose groups show a higher incidence than control groups.
3. The sponsor should complete a full histological examination of all tissues and organs in future toxicity studies.

4. The submitted pilot Segment I reproduction toxicity study in rats consisted of a 3-week pre-mating administration interval in males. It should be noted that ICH Guidelines for Detection of Toxicity to Reproduction (ICH S5A and S5B) recommend pre-mating administration for males to be 4-weeks in duration, assuming that a toxicity study of at least 1-month duration demonstrates no effects on spermatogenesis (pre-mating administration of 9-10 weeks in the case of positive findings). The sponsor should consult the ICH Guidelines when performing the definitive Segment I and other reproductive toxicology studies.
5. The sponsor should submit a complete report of the Segment II reproduction toxicology study in rabbits (Study No. P-6802) when it becomes available.

Timothy J. McGovern, Ph.D., Pharmacologist

Draft Comments for Letter to Sponsor:

Original IND 55,364

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/P. Honig
HFD-570/G. Trout
HFD-570/T.J. McGovern