

**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
	<b>SCH 34117</b>							
C <sub>max</sub> (ng/ml)	500	770	769	1424	1209	2696	311	2894
T <sub>max</sub> (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
	<b>SCH 29851</b>							
C <sub>max</sub> (ng/ml)							348	104
T <sub>max</sub> (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

\* 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
Adrena's	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 (sternum)	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

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**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, chromorhinorrhea 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.

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Timothy J. McGovern, Ph.D., Pharmacologist

Attachment I.  
Attachment II.  
Attachment III.

Original IND \_\_\_\_\_

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:**

Please clarify the term "mineralization" as related to findings in the ovaries of monkeys (i.e., type of minerals) in the 3 month toxicity study (Study P-6976).

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**HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS  
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Review #5**

IND No. ——— Serial No. 051 Submission Date: 26 APR 1999  
094 01 NOV 1999

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

Review Completed: 07 JUN

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

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

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

Study	Report #	Serial #
<i>Safety Pharmacology:</i>		
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 <sup>+</sup> 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
<i>Pharmacokinetics:</i>		
SCH 34117: A study of the tissue distribution of radioactivity in male and female sprague dawley rats and <del>rats</del> rats following a single oral dose of <sup>14</sup> C-SCH 34117	P-6741	094

**Studies Not Reviewed in this IND:**

[ ]

**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 V<sub>max</sub> 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<sup>+</sup> 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<sup>-6</sup> M as the concentration at

which  $\frac{1}{2}$  current is blocked ( $k_{0.5}$ ) was  $5 \times 10^{-6}$  M ( $k_{0.5}$  for loratadine was  $8.7 \times 10^{-6}$ ). SCH 34117 had no effect at  $10^{-5}$  M on inward rectifier current ( $i_{K1}$ ) although the curve was flatter at  $3 \times 10^{-5}$  M; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters at concentrations ranging from 5-100  $\mu$ M.

**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 <math>\mu</math>M and 10 <math>\mu</math>M, respectively, after 30 minutes); experiments prematurely terminated after 50 <math>\mu</math>M due to sustained ventricular fibrillation; NOEL = 1 <math>\mu</math>M.</p> <p>QT increase at 10 <math>\mu</math>M 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 <math>\mu</math>M 2 hours after dosing; increased up to 34% at 0.5 <math>\mu</math>M after 3 hours; NOEL = 0.2 <math>\mu</math>M.</p> <p>No effect of SCH 34117 alone on JT interval. Produced nearly two-fold increase in JT interval at 0.5 <math>\mu</math>M in combination with quinidine compared to quinidine alone (15%).</p> <p>Loratadine (up to 50 <math>\mu</math>M) had no effect on QT, QRS or JT intervals</p>
Perfused guinea pig left ventricular papillary muscle	<p><b>Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.</b></p> <p>No effect on resting potential or action potential duration at drug concentration of 10, 30 or 100 <math>\mu</math>M.</p> <p>SCH 34117 decreased <math>V_{max}</math> at <math>\geq 30</math> <math>\mu</math>M with pacing at 1 Hz; decrease of 57% at 100 <math>\mu</math>M. Associated with decrease in velocity of impulse conduction and increase in excitation threshold. Decrease in <math>V_{max}</math> 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 <math>\mu</math>M (decreased isometric force to 70% of pre-drug level at 1 Hz).</p>
Isolated rabbit ventricular myocytes	<p><b>Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.</b></p> <p><b>Drug listed in report as IN 0132, assumed to be Loratadine.</b></p> <p>Effects on <math>Na^+</math> current: SCH 34117 (100 <math>\mu</math>M; 5-10 min) reduced <math>Na^+</math> current at holding potentials of -100 to -80 mV more effectively than 100 <math>\mu</math>M loratadine. Loratadine showed preferential binding to channel in inactivated state.</p> <p>Effects on delayed rectifier current (<math>i_{Kr}</math>): SCH 34117 (<math>6 \times 10^{-6}</math> M) reduced <math>i_{Kr}</math> current to <math>\sim \frac{1}{2}</math> control value at 10 mV. Only small remnant of <math>i_{Kr}</math> current visible at <math>3 \times 10^{-5}</math> M. Concentration at which <math>\frac{1}{2}</math> current is blocked (<math>k_{0.5}</math>) = <math>5 \times 10^{-6}</math> M. <math>k_{0.5}</math> for loratadine = <math>8.7 \times 10^{-6}</math> M</p> <p>Effect on inward rectifier current (<math>i_{K1}</math>): no effect at <math>10^{-5}</math> M; IV curve flatter at <math>3 \times 10^{-5}</math> M. Loratadine had more pronounced effect than SCH 34117 and was more slowly reversible.</p>

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**PHARMACOKINETICS AND TOXICOKINETICS:**

Pharmacokinetic parameters in rats following oral (gavage) administration are summarized in Table 2. The C<sub>max</sub> 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 (— 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 <sub>max</sub> (µg equiv/g)	0.648	0.426
T <sub>max</sub> (hr)	6	3
AUC(tf) (µg equiv.hr/g)	13.9	7.65
	SCH 34117	
C <sub>max</sub> (µg/ml)	0.0995	0.259
T <sub>max</sub> (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 <sup>14</sup>C-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.

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**Table 3.** Tissue distribution of  $^{14}\text{C}$ -SCH 34117 in rats after single oral gavage administration.

Tissue	Males (6 hrs)		Females (3 hrs)	
	Total radioactivity ( $\mu\text{g equiv/g}$ )	Tissue:Plasma ratio	Total radioactivity ( $\mu\text{g equiv/g}$ )	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  $\text{---}$  to  $\text{---}$   $\mu\text{g equiv/g}$  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 ( $\mu\text{g equiv/g}$ )	Tissue:Plasma ratio
Plasma	0.795	$\text{---}$
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  $^{14}\text{C}$ -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  $\text{CO}_2$  (0.06-0.36%).

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## OVERALL SUMMARY AND EVALUATION

**Safety Pharmacology:** SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10  $\mu$ M) in isolated rabbit hearts, due primarily to increasing the QRS complex up to 5-6-fold. SCH 34117 did not increase JT interval alone but did enhance a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50  $\mu$ M. SCH 34117 also decreased Vmax and velocity of impulse conduction and increased excitation threshold ( $\geq$  30  $\mu$ M) while producing a negative inotropic effect (10  $\mu$ M) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100  $\mu$ M. In isolated rabbit ventricular myocytes, SCH 34117 (100  $\mu$ M) reduced Na<sup>+</sup> current more effectively than 100  $\mu$ M loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) current to  $\sim$  1/2 control value at  $6 \times 10^{-6}$  M as the concentration at which 1/2 current is blocked (k0.5) was  $5 \times 10^{-6}$  M (k0.5 for loratadine was  $8.7 \times 10^{-6}$ ). SCH 34117 had no effect at  $10^{-5}$  M on inward rectifier current (iK1) although the curve was flatter at  $3 \times 10^{-5}$  M; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters in vitro at concentrations ranging from  $\sim$   $\mu$ M. SCH 34117 was previously shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K<sup>+</sup> 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 Cmax 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 <sup>14</sup>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 <sup>14</sup>C-SCH 34117 was excreted primarily in feces.

**RECOMMENDATION**

None at this time.

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND \_\_\_\_\_

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HFD-570/T.J. McGovern

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**HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS  
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Review #6**

IND No. : \_\_\_\_\_ 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>
<b><i>Sub-chronic Toxicology:</i></b>		
Three-month dose-range finding study of SCH 34117 in mice	SN 97253	44.6
<b><i>Genetic Toxicology:</i></b>		
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 (\_\_\_\_\_ submitted to NDA 21-165) was submitted to IND \_\_\_\_\_. 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 # \_\_\_\_\_  
 \_\_\_\_\_ or \_\_\_\_\_ 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 (CrI/CD-1 BR VAF/Plus; 6 weeks old, 18.9-31 g) were assigned to the following treatment groups:

Dose	Veh.	24	48	96	192
(mg SCH 34117/kg/day):	Control				
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 (mg SCH 34117/kg/day):	0	24	48	96	192
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 Dose (mg/kg)	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.

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

Dose (mg SCH 34117/kg/day):	0	24	48	96	192
<b>Males</b>					
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
<b>Females</b>					
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.**

	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
Hematology	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.

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**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.

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

Organ weight	Males				Females			
	24	48	96	192	24	48	96	192
Dose group (mg/kg)								
Liver								
AOW-% $\Delta$ from control	5	6	15	29	7	13	36	40
RTB-% $\Delta$ from control	5	12	26	71	6	11	34	69
Lungs								
AOW-% $\Delta$ from control	5	-5	5	10	no $\Delta$	6	11	11
RTB-% $\Delta$ from control	5	no $\Delta$	14	46	1	1	8	36
Thymus								
AOW-% $\Delta$ from control	-7	-7	-17	-41	-29	3	-19	-47
RTB-% $\Delta$ from control	-7	-2	-10	-22	-30	1	-21	-36
Uterus								
AOW-% $\Delta$ from control					-14	-18	-33	-48
RTB-% $\Delta$ 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.

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Table 9. Histological changes in mice following 3-month administration.

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
Brain – vacuolation of choroid plexus	10	0	10	10	10	10	0	0	10	10
Minimal	0		0	0	5	0			0	6
Mild	0		0	0	4	0			0	4
Moderate	0		0	0	1	0			0	0
Bone marrow – Vacuolation– macrophage	10	0	0	10	10	10	0	0	10	10
minimal	0			0	2	0			0	3
mild	0			0	6	0			0	5
moderate	0			0	1	0			0	1
Atrophy, fat										
Minimal	0			0	0	0			0	1
Epididymides	10	0	10	10	10					
Cellular debris, increased										
Minimal	0		0	0	4					
Mild	0		0	0	1					
Single cell necrosis, epithel.										
Minimal	0		0	0	3					
Mild	0		0	0	1					
Granuloma, sperm										
Mild	0		0	0	1					
Vacuolation, epithelium										
Minimal	0		0	7	0					
Mild	0		0	1	4					
Moderate	0		0	0	6					
Oligospermia										
Mild	0		0	0	1					
Eyes –	10	10	10	10	10	10	10	10	10	10
Vacuolation, retinal, epithelium										
minimal	0	0	2	8	1	0	0	3	7	1
mild	0	0	0	1	3	0	0	0	3	6
moderate	0	0	0	1	3	0	0	0	0	1
Gall bladder–	10	9	9	9	9	10	10	10	10	10
Vacuolation, epithelium										
minimal	0	0	0	0	1	0	0	0	0	3
mild	0	0	0	0	1	0	0	0	0	0
Heart	10	0	10	10	10	10	0	10	10	10
Vacuolation, myofiber,										
Minimal	0		0	6	4	0		0	5	3
Mild	0		0	0	6	0		0	0	7
Necrosis, myofiber										
Minimal	0		0	0	2	0		0	0	1
Kidneys	10	10	10	10	10	10	10	10	10	10
Vacuolation, epithelium										
Minimal	0	0	5	4	2	0	3	3	3	0
Mild	0	0	0	5	3	0	0	4	5	5
Moderate	0	0	0	1	5	0	0	3	2	5
Necrosis, epithelium										

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
Minimal	0	0	0	2	3	0	0	0	0	4
Mild	0	0	0	0	3	0	0	0	0	0
Lymph nodes	10	0	10	10	10	10	0	0	10	10
Vacuolation, macrophage mandibular										
Minimal	0		0	0	0	0			0	3
Vacuolation, macrophage mesenteric										
Minimal	0		0	6	0	0			6	1
Mild	0		0	0	8	0			0	7
Moderate	0		0	0	2	0			0	2
Necrosis, lymphoid, mandibular										
Mild	0		0	0	0	0			0	1
Liver	10	10	10	10	10	10	10	10	10	10
Vacuolation, kupfer cell										
Minimal	0	0	0	0	4	0	0	0	0	6
Mild	0	0	0	0	4	0	0	0	0	2
Moderate	0	0	0	0	1	0	0	0	0	0
Vacuolation, centrilob., hepatocellular										
Minimal	0	0	6	7	7	0	0	0	0	6
Mild	0	0	0	2	0	0	0	0	0	4
Moderate	0	0	0	0	3	0	0	0	0	0
Hypertrophy, centrilob										
Minimal	0	0	5	4	7	0	0	0	0	6
Mild	0	0	1	5	0	0	0	0	0	4
Moderate	0	0	0	0	3	0	0	0	0	0
Lungs	10	0	10	10	10	10	0	10	10	10
Accumulation, alv macrophage										
Minimal	0		0	0	3	0		0	1	2
Mild	0		0	0	6	0		0	0	6
Moderate	0		0	0	1	0		0	0	2
Vacuolation, alv macroph										
Minimal	0		0	0	6	0		0	0	2
Mild	0		0	0	3	0		0	0	8
Moderate	0		0	0	1	0		0	0	0
Vacuolation, epithelium										
Minimal	0		0	10	8	0		0	9	1
Mild	0		0	0	2	0		0	0	9
Crystal, eosinophilic										
Minimal	0		0	0	4	0		0	0	6
Mild	0		0	0	1	0		0	0	1
Moderate	0		0	0	0	0		0	0	1
Esophagus	10	0	10	10	10	10	0	10	10	10
Vacuolation, myofiber										
minimal	0		0	4	5	0		0	1	2
mild	0		0	0	5	0		0	0	7
moderate	0		0	0	0	0		0	0	1
Ovaries						10	0	2	10	10
Vacuolation, sex cord										
Mild						0	0	0	0	5

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
Moderate Vacuolation, corp lutea						0	0	0	0	5
Minimal						0	0	0	0	1
Mild						0	0	0	0	2
Moderate Necrosis, granulosa cell						0	0	0	0	6
Minimal						0	0	0	0	4
Mild						0	0	0	0	3
Moderate						0	0	0	0	2
Pancreas Vacuolation, epithelium exocrine	10	0	0	10	10	10	0	0	10	10
Minimal	0			0	2	0			0	2
Mild	0			0	8	0			0	8
Parathyroid glands Vacuolation, chief cell	10	0	7	7	10	10	0	9	10	10
Minimal	0		0	0	2	0		0	0	0
Pituitary gland Vacuolation, pars anterior	10	0	10	9	10	10	0	9	10	10
Minimal	0		0	6	7	0		0	7	4
Mild	0		0	0	3	0		0	0	5
Moderate	0		0	0	0	0		0	0	1
Salivary gland Vacuolation, ductular	10	0	0	10	10	10	0	0	10	10
Minimal	0			0	5	0			0	5
Mild	0			0	1	0			0	1
Vacuolation, acinar										
Minimal	0			0	0	0			0	0
Atrophy, sublingual										
Mild	0			0	0	0			0	0
Cellular infiltration, mononuclear cell										
Minimal	0			0	0	0			0	0
Seminal vesicles Vacuolation, epithelium	10	1	0	10	10					
Mild	0	0		0	10					
Skeletal muscle Vacuolation, myofiber	10	0	0	10	10	10	0	0	10	10
Minimal	0			0	7	0			0	2
Mild	0			0	3	0			0	6
Moderate	0			0	0	0			0	2
Necrosis, myofiber										
Minimal	0			0	1	0			0	2
Skin Vacuolation, epithelium	10	10	10	10	10	10	10	10	10	10
Minimal	0	0	0	4	2	0	0	0	4	1
Mild	0	0	0	0	5	0	0	0	0	6
Moderate	0	0	0	0	0	0	0	0	0	3
Panniculitis, granulomatous mild										
	0	0	0	0	1	0	0	0	0	0

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
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
Mild	0		0	0	2	0		0	0	2
Necrosis, lymphoid										
Minimal	0		0	1	2	0		0	0	3

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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	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, m-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						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:

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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 ~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  $5 \times 10^8$  cells/ml for *Salmonella typhimurium* strain, and approximately  $15 \times 10^8$  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  $\mu\text{g}/\text{plate}$  and above for TA 97a, 63  $\mu\text{g}/\text{plate}$  for TA 100, 125  $\mu\text{g}/\text{plate}$  for TA 98, and at 500  $\mu\text{g}/\text{plate}$  and above for TA 1535 and WP2uvrA. Microcolonies were observed at 63 and 125  $\mu\text{g}/\text{plate}$  for TA 102, at 125 and 250  $\mu\text{g}/\text{plate}$  for TA 1535, at 250  $\mu\text{g}/\text{plate}$  and above for TA 98, and at 125  $\mu\text{g}/\text{plate}$  and above for TA 100. Cytotoxicity to background lawn was observed at 16  $\mu\text{g}/\text{plate}$  and above for TA 98, at 63  $\mu\text{g}/\text{plate}$  and above for TA 1535, at 125  $\mu\text{g}/\text{plate}$  and above for TA 100, at 250  $\mu\text{g}/\text{plate}$  and above for TA 98 and at 2000  $\mu\text{g}/\text{plate}$  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  $\mu\text{g}/\text{plate}$  and above for TA 97a, 250  $\mu\text{g}/\text{plate}$  and above for TA 100 and 102, 500  $\mu\text{g}/\text{plate}$  for TA 98, and at 1000  $\mu\text{g}/\text{plate}$  and above for WP2uvrA. Microcolonies were observed at 500  $\mu\text{g}/\text{plate}$  for TA 98 and at 1000  $\mu\text{g}/\text{plate}$  for TA 1535. Cytotoxicity to background lawn was observed at 500  $\mu\text{g}/\text{plate}$  for both TA 100 and TA 98, at 1000  $\mu\text{g}/\text{plate}$  for TA 1535, and at 2000  $\mu\text{g}/\text{plate}$  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  $\mu\text{g}/\text{plate}$  and above for TA 97a, and at 125  $\mu\text{g}/\text{plate}$  for TA 102. Microcolonies were observed at 500  $\mu\text{g}/\text{plate}$  for TA 1535. Cytotoxicity to background lawn was observed at 125  $\mu\text{g}/\text{plate}$  for both TA 97a and 102, and at 250  $\mu\text{g}/\text{plate}$  and above for TA 1535.

Thus, SCH 45581, up to 1000  $\mu\text{g}/\text{plate}$  in *Salmonella* strains and up to 2000  $\mu\text{g}/\text{plate}$  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 CrI:CD-1 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.

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F. Timothy J. McGovern, Ph.D.,  
Pharmacologist

Addendum 1: Histopathology inventory for SCH 34117.

IND \_\_\_\_\_  
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

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**Addendum 1: Histopathology inventory for IND** \* 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	X
Bone (femur)	X		X	X	X	X	X	X
Bone (tibia)					X	X		
Bone (sternum)	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*
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*	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

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**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 \_\_\_\_\_ 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 "\_\_\_\_\_" be replaced by "\_\_\_\_\_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 <sup>14</sup>C-loratadine or <sup>14</sup>C-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 \_\_\_\_\_antagonist with selective H<sub>1</sub>-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 H<sub>1</sub> receptor. Desloratadine \_\_\_\_\_

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Draft

Labeling



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

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Studies	DCL AUC	DCL+ DCL metabolites AUC	Animal:human ratio	PB correction	derivation of animal AUC
<b>Human - 5 mg</b>	56.9	711.25			
<b>rat: fertility</b>					
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
<b>rat: embryo fetal</b>					
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
<b>rat: Seg III</b>					
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
<b>rabbit: embryo-fetal</b>					
60 mg/kg	12987	NA	228	NA	Embryo-fetal rabbit study
<b>Overdosage</b>					
rat-250 mg/kg	27441	124731.82	175	116	1-week Pk study at 240 mg/kg; M+F
<b>Carcinogenicity</b>					
Mouse - 40 mg/kg	1861	5029.73	7	3	28-day dietary study w/loratadine
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/loratadine
Rat - 10 mg/kg	1619	7359.09	10	7	28-day dietary study w/loratadine
<b>QTc:</b>					
Monkey - 24 mg/kg	54346	NA	955		3-mos monkey (P6976) at 24 mg/kg
<b>Species</b>	<b>DCL/14C ratio</b>	<b>Protein binding (%)</b>			
Mouse	0.37	94.4			
Rat	0.22	90.5			
Human	0.08	85.6			
Monkey	NA	85.8			

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Timothy J. McGovern, Ph.D.

NDA 21-312

Drug: **Clarinet**

	age	# daily		mg/day	kg	mg/kg	factor	mg/m <sup>2</sup>
		mg/dose	doses					
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 <sup>2</sup>	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			---	---	---	---	---	---

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

NDA No. 21-165 Submission Date: 04 OCT 2000  
Reviewer: Timothy J. McGovern, Ph.D. Review Completed: 09 NOV 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 which they requested a change to the **Mechanism of Action:** section.

**LABELING REVIEW:**

In the section entitled "Clinical Pharmacology" and subsection entitled "Mechanism of Action:", the sponsor proposes that the sentence \_\_\_\_\_  
\_\_\_\_\_ As originally described in the Original Pharmacology/Toxicology NDA Review dated 9/29/2000, a submitted reference (Genovese *et al*, 1997) demonstrated that pre-incubation of purified (16-74%) human FcεRI<sup>+</sup> cells from peripheral blood and skin cells with desloratadine ( $3 \times 10^{-6}$  –  $10^{-4}$ M) induced a concentration-dependent inhibition of histamine release following challenge with anti-FcεRI. Previous claims made by the sponsor related to \_\_\_\_\_ were deleted since it was difficult to place the statements in a clinical context. However, the Medical Reviewers determined that the currently proposed statement, if substantiated, is acceptable with minor changes to the wording to provide consistency with other approved antihistamines. Although it is unclear that this *in vitro* response is representative of the *in vivo* setting, the sponsor's proposal is acceptable with slight changes to the actual wording of the statement. Thus, the following changes should be made to the label:

**MECHANISM OF ACTION:**

Desloratadine is a long acting tricyclic \_\_\_\_\_ antagonist with selective H<sub>1</sub>-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 H<sub>1</sub> receptor. \_\_\_\_\_

\_\_\_\_\_ -Desloratadine  
inhibited histamine release from human mast cells *in vitro*.

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  
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HFD-540/B. Hill  
HFD-590/K. Hastings

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**PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION****IND number:** \_\_\_\_\_**Review number:** 2**Sequence number/date/type of submission:** 021/15 DEC 2000/Info Tox  
023/18 APR 2001/Info Tox  
024/20 APR 2001/Info Tox**Information to sponsor:** Yes ( ), No (✓)**Sponsor and/or agent:** Schering-Plough Corp., Kenilworth, NJ**Manufacturer for drug substance:** \_\_\_\_\_**Reviewer name:** Timothy J. McGovern, Ph.D.**Division name:** Pulmonary and Allergy Drug Products**HFD #:** 570**Review completion date:** August 30, 2001**Drug:****Trade name:** Clarinex rapidly disintegrating tablets**Generic name:** NA**Code name:** SCH 34117**Chemical name:** 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)**CAS registry number:** NA**Mole file number:** NA**Molecular formula/molecular weight:** C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>/310.82**Relevant INDs/NDAs/DMFs:** IND \_\_\_\_\_ IND \_\_\_\_\_  
\_\_\_\_\_, NDA 19-658 (Loratadine Tablet), NDA 20-704 (Loratadine  
RediTabs), IND \_\_\_\_\_, IND \_\_\_\_\_*Drug Class: Antihistamine***Indication:** Seasonal allergic rhinitis and chronic idiopathic urticaria

<b>Clinical Formulation:</b>	<b>Ingredient</b>	<b>mg/tablet</b>
	SCH 37114	5
	Gelatin Type B NF/Ph./Eur.	}
	Mannitol USP	
	Aspartame	
	Polacrillin potassium	
	Dye _____Red _____	
	Flavor Tutti-Frutti _____	
	Citric acid USP	

**Route of administration:** Oral

**Proposed clinical protocol:** None. Two protocol concept sheets were submitted for review.

**Previous Clinical Experience:** SCH 34117 has been assessed in numerous clinical trials using various formulations including the rapidly disintegrating tablet.

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

**Preclinical studies reviewed in these submissions:**

SN 99290: Mucous membrane irritation study of SCH 34117 (desloratadine) RediTab Tablets in the hamster cheek pouch. Submission 021

SN 00479: Mucous membrane irritation of SCH 34117 RediTab Tablets in the hamster cheek pouch. Submission 023

SN 00480: Mucous membrane irritation of SCH 34117 RediTab Tablets in the hamster cheek pouch. Submission 024

**Preclinical studies not reviewed in these submissions:** None

**Introduction and drug history:** Desloratadine (SCH 34117) is the active metabolite of loratadine and has an antihistaminic potency of 2.5-20 times that of loratadine. Tablet, \_\_\_\_\_ and rapidly disintegrating tablet formulations have all been approved for loratadine.

The sponsor submitted two oral mucosa irritation studies in hamsters using a formulation referred to as \_\_\_\_\_ in order to assess the irritancy potential of the SCH 34117 RediTab tablet. It is unclear if the formulations were similar in both studies.

The sponsor also submitted a hamster oral mucosa irritation study using \_\_\_\_\_. The study was performed to investigate one formulation found \_\_\_\_\_ than the RediTab formulation that is the subject of NDA 21-312. The sponsor plans to assess the effects of 5 mg desloratadine \_\_\_\_\_ formulation in humans through two clinical pharmacology studies (protocol concept sheets for protocols P02393 and P02430) to evaluate the bioequivalence of 5 mg desloratadine \_\_\_\_\_ formulation and a 5 mg CLARINEX tablet and the potential irritation of the 5 mg desloratadine \_\_\_\_\_ formulation during 14 days of treatment. The sponsor plans to develop \_\_\_\_\_

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**SPECIAL TOXICOLOGY STUDIES:**

**Study title:** Mucous membrane irritation of SCH 34117 (desloratadine) reditab tablets in the hamster cheek pouch

**Key study findings:** Drug-related observations during this 5-day study included very slight to slight redness in all hamsters treated with 5 mg SCH 34117 RediTab from the first day of dosing onward. Severity did not increase with dosing duration. Death in one drug-treated animal was attributed to a possible toxic effect of the drug with the isoflurane anesthesia.

**Study no:** SN 99290

**Volume #, and page #:** 4.1, 1

**Conducting laboratory and location:** Schering Plough, Lafayette, NJ

**Date of study initiation:** July 1999

**GLP compliance:** The report included a signed GLP report

**QA report:** yes (✓) no ( )

**Drug, lot #, radiolabel, and % purity:** SCH 34117 reditab tablet, batch # 39554-152, purity not reported

**Formulation/vehicle:** not stated, assumed to correspond to above noted clinical formulation

**Methods:** Prior to dosing, each hamster was anesthetized with isoflurane for one-hour prior to and during dosing. Anesthesia was maintained for at least 10 minutes after dosing for observation of the cheek pouch. A small amount of sterile water was added to the dosed cheek pouch just prior to insertion of the tablet. Tablets were inserted in the left cheek pouch. The contralateral cheek pouch served as an untreated control.

**Dosing:**

Species/strain: Golden Syrian Hamsters (SYR)BR VAF/Plus)

#/sex/group or time point (main study): 6 females

Satellite groups used for toxicokinetics or recovery: NA

Age: 10-11 weeks

Weight: 115.8-141 g

Doses in administered units: 6 females were treated as sham controls and underwent physical manipulation of the cheek pouch. Hamsters received four 5-mg SCH 34117 tablets on day 0 at 10 minute intervals, two tablets on day 1 and one tablet thereafter for the remaining 3 dosing days. The sponsor states that the initial dose of 4 tablets was reduced due to a possible toxic effect of SCH 34117 in combination with isoflurane anesthesia as indicated by a longer recovery time from anesthesia compared with controls.

Route, form, volume, and infusion rate: transmucosal, tablet for 5 consecutive days

**Observations and times:**

Clinical signs:	Not assessed
Body weights:	Day 0
Gross pathology:	Day 5 following observation period. Both cheek pouches of each hamster were dissected free from the surrounding tissues, opened longitudinally, examined and fixed in buffered formalin.
Organs weighed:	Not assessed
Histopathology:	Day 5 following observation period. Six transverse sections of each cheek pouch, 3 from proximal end and 3 from distal end were processed and examined microscopically.
Other:	Mucous membrane irritation, 2x daily (immediately prior to and 10 minutes after dosing)

**Results:**

**Mortality:** One SCH 34117-dosed hamster was found dead on day 3. Cause of death was not determined but was attributed to a possible toxic effect of the drug with the isoflurane anesthesia.

**Mucous membrane irritation:** Results are summarized in the table below. No findings were noted prior to dosing on Days 0 through 3 of dosing. One SCH 34117-treated animal displayed very slight redness prior to dosing on Day 4. At 10 minutes after dosing, very slight redness was noted on Day 0 in SCH 34117-treated cheek pouches of all hamsters; on Day 1 very slight (5/6) to slight redness (1/6) was noted. Five of six SCH 34117-treated animals demonstrated very slight redness on Day 2 and five of five animals demonstrated very slight to slight redness on Days 3 and 4. No irritation was observed in sham animals while one SCH 34117-treated animal demonstrated very slight redness in the untreated cheek pouch on days 2 and 4 (animals 8 and 10, respectively).

**Gross pathology:** No significant drug-related findings were noted.

**Histopathology:** No significant drug-related findings were noted.

**Summary of individual study findings:** Drug-related observations included very slight to slight redness in all female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab from the first day of dosing onward. Severity did not increase with dosing duration. One drug-treated animal died and the death was attributed to a possible toxic effect of the drug with the isoflurane anesthesia; doses were 385-1541 times the human dose on a mg/kg basis. No drug-related gross or microscopic findings were noted.

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SCH 34117  
TOXICOLOGY

STUDY NO. 99290

**Table 1 Individual Mucous Membrane Irritation Scores<sup>a</sup>**

Hamster No.	Day of Dosing <sup>b</sup>																			
	0				1				2				3				4			
	Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Sham Control																				
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SCH 34117 Reditab Tablet (5 mg)																				
7	0	0	±	0	0	0	±	0	0	0	±	0	0	0	±	0	0	0	1	0
8	0	0	±	0	0	0	±	0	0	0	±	±	0	0	±	0	0	0	±	0
9	0	0	±	0	0	0	±	0	0	0	0	0	0	0	1	0	0	0	±	0
10	0	0	±	0	0	0	1	0	0	0	±	0	0	0	1	0	0	0	±	±
11	0	0	±	0	0	0	±	0	0	0	±	0	0	0	1	0	0	0	±	±
12	0	0	±	0	0	0	±	0	0	0	±	0	0	0	1	0	0	0	±	0

L = Left cheek pouch    R = Right cheek pouch    FD = Found Dead

a: Grading Scale for Mucous Membrane Irritation

0 = No reaction

± = Very slight (barely perceptible) redness, usually nonconfluent

1 = Slight (well defined) redness, usually confluent

2 = Moderate redness

3 = Severe redness, with or without edema, necrosis or scab formation

b: SCH 34117-dosed hamsters received four tablets on Day 0, two tablets on Day 1, and one tablet thereafter. The initial dose of four tablets was reduced due to a possible toxic effect of SCH 34117 in combination with isoflurane anesthesia; this was indicated by a longer recovery time from anesthesia compared with controls.

**Study title:** Mucous membrane irritation of SCH 34117 rediva tablets in the hamster cheek pouch

**Key study findings:** Very slight redness of the mucous membrane was observed in 4 of 6 female Syrian hamsters treated with 5 mg SCH 34117 RediTab with the formulation during the course of the 5-day study. Incidence diminished as the study progressed.

**Study no:** SN 00479

**Volume #, and page #:** 1, 1

**Conducting laboratory and location:** Schering Plough, Lafayette, NJ

**Date of study initiation:** November, 2000

**GLP compliance:** The report included a signed GLP report

**QA report:** yes (✓) no ( )

**Drug, lot #, radiolabel, and % purity:** SCH 34117, batch # 24180J917, purity not reported

**Formulation/vehicle:** Cover letter states that the objective of this study was to assess the irritation potential of SCH 34117 RediTab tablets. Although this statement implies that the formulation differs from the originally proposed formulation, the sponsor did not provide formulation data for this batch.

**Methods:** Prior to dosing, each hamster was anesthetized with isoflurane for one-hour prior to and during dosing. Anesthesia was maintained for at least 10 minutes after dosing for observation of the cheek pouch. A small amount of sterile water was added to the dosed cheek pouch just prior to insertion of the tablet. Tablets were inserted in the left cheek pouch. The contralateral cheek pouch served as an untreated control.

**Dosing:**

Species/strain: Golden Syrian Hamsters [SYR]BR VAF/Plus)

#/sex/group or time point (main study): 6 females

Satellite groups used for toxicokinetics or recovery: NA

Age: 8 weeks

Weight: 113-127 g

Doses in administered units: 6 females were treated as sham controls and underwent physical manipulation of the cheek pouch. 5 mg (39-44 mg/kg) was administered daily

Route, form, volume, and infusion rate: transmucosal, 1 tablet for 5 consecutive days

**Observations and times:**

Clinical signs: 1 time daily

Body weights: Day 0

Gross pathology: Day 5 following observation period. Both cheek pouches of each hamster were dissected free from the surrounding tissues, opened longitudinally, examined and fixed in buffered formalin.

Histopathology: Day 5. Six transverse sections of each cheek pouch, 3 from proximal end and 3 from distal end, were processed and examined microscopically.

Other: Mucous membrane irritation, 2x daily (immediately prior to and 10 minutes after dosing)

**Results:**

Mortality: All hamsters survived dosing procedure.

Clinical signs: No significant observations were noted.

Mucous membrane Irritation: Results are summarized in the table below. No findings were noted before dosing on Days 0 through 4 of dosing or 10 minutes after dosing on Days 0 and 1. Very slight redness was noted in SCH 34117-treated cheek pouches 10 minutes after dosing in 3 hamsters on Day 2 in 2 hamsters on Day 3 and 1 hamster on day 4. No irritation was observed in sham animals or in the untreated cheek pouches of treated hamsters.

Gross pathology: No significant drug-related findings were noted.

Histopathology: No significant drug-related findings were noted.

**Summary of individual study findings:** Very slight redness of the mucous membrane was observed in 4 of 6 female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab with the formulation during the course of the 5-day study. Incidence diminished as the study progressed. No drug-related gross or microscopic findings were noted.

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Table 1 Individual Mucous Membrane Irritation Scores <sup>a</sup>																					
Hamster No. / Sex		Day																			
		0				1				2				3				4			
		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose	
		L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R		
Sham Control																					
1F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
2F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
3F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
4F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
5F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
6F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
SCH 34117 Reditab Tablet (5 mg)																					
7F		0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	0	0		
8F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
9F		0	0	0	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0		
10F		0	0	0	0	0	0	0	0	0	0	±	0	0	0	±	0	0	0		
11F		0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	0	±		
12F		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

L = Left cheek pouch, R = Right cheek pouch

a: Grading Scale for Mucous Membrane Irritation

0 = No reaction

± = Very slight (barely perceptible) redness, usually nonconfluent

1 = Slight (well defined) redness, usually confluent

2 = Moderate redness

3 = Severe redness, with or without edema, necrosis or scab formation



Route, form, volume, and infusion rate: transmucosal, 1 tablet for 5 consecutive days

**Observations and times:**

Clinical signs:	1 time daily
Body weights:	Day 0
Gross pathology:	Day 5 following observation period. Both cheek pouches of each hamster were dissected free from the surrounding tissues, opened longitudinally, examined and fixed in buffered formalin.
Histopathology:	Day 5. Six transverse sections of each cheek pouch, 3 from proximal end and 3 from distal end, were processed and examined microscopically.
Other:	Mucous membrane irritation, 2x daily (immediately prior to and 10 minutes after dosing)

**Results:**

Mortality: All hamsters survived dosing procedure.

Clinical signs: No significant observations were noted.

Mucous membrane Irritation: Results are summarized in the table below. No findings were noted on Day 0 of dosing. On day 1 pre-dose, one animal demonstrated slight irritation with pale, raised areas in the drug-treated cheek. At 10 minutes after dosing on day 1, 4 of 6 treated animals displayed very slight to slight irritation in the drug-treated pouches. Two had blister-like and pale, raised areas. By day 2, 5 of 6 had very slight to moderate irritation with pale, raised areas and/or blister-like raised areas in drug-treated pouches. The degree of irritation had increased to slight to severe by day 3 with blisters in 4 of 6 animals. Two animals had thickened, abraded areas in the left corner of the mouth. By day 4, irritation was moderate to severe in 4 of 6 animals. No irritation was observed in sham animals or in the untreated cheek pouches of treated hamsters.

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**Table 1 Individual Mucous Membrane Irritation Scores<sup>a</sup>**

Hamster No./ Sex	Day of Dosing																			
	0				1				2				3				4			
	Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose		Predose		Postdose	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
<b>Sham Control</b>																				
1F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>SCH 34117 Reditab Tablet (5 mg)</b>																				
7F	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0	0	0	0	0	0
8F	0	0	0	0	0	0	1 <sup>b,c</sup>	0	± <sup>c</sup>	0	1 <sup>c</sup>	0	3 <sup>c</sup>	0	3 <sup>c</sup>	0	3 <sup>c</sup>	0	3 <sup>c</sup>	0
9F	0	0	0	0	0	0	±	0	0	0	±	0	2 <sup>c</sup>	0	2 <sup>c</sup>	0	3 <sup>c</sup>	0	3 <sup>c</sup>	0
10F	0	0	0	0	0	0	0	0	± <sup>c</sup>	0	± <sup>c</sup>	0	1 <sup>c,d</sup>	0	1 <sup>c,d</sup>	0	2 <sup>c</sup>	0	2 <sup>c,d</sup>	0
11F	0	0	0	0	1 <sup>b</sup>	0	1 <sup>b,c</sup>	0	± <sup>b,c</sup>	0	2 <sup>b,c</sup>	0	3 <sup>c</sup>	0	3 <sup>c,d</sup>	0	3 <sup>c</sup>	0	3 <sup>c,d</sup>	0
12F	0	0	0	0	0	0	±	0	0	0	0	0	0 <sup>d</sup>	0	0 <sup>d</sup>	0	0	0	0	0

L = Left cheek pouch      R = Right cheek pouch

a: Grading Scale for Mucous Membrane Irritation  
 0 = No reaction  
 ± = Very slight (barely perceptible), redness usually nonconfluent  
 1 = Slight (well defined) redness, usually confluent  
 2 = Moderate redness  
 3 = Severe redness, with or without edema, necrosis or scab formation

b: Pale, raised areas  
 c: Blister-like areas (with or without abrasions)  
 d: Corner of mouth thickened and abraded

Gross pathology: The treated cheek pouches contained pink material interpreted by the sponsor as undissolved Reditab tablet (see Table below). Discoloration of the cheek pouch was noted in 2 hamsters.

Histopathology: Microscopic changes in the SCH 34117-treated group included ulceration, necrosis, inflammation and fibroplasia of the oral cavity (see Table below). Findings were of minimal to moderate severity.

Gross/microscopic changes following 5 day administration of SCH 34117 RediTabs

Observed signs	Dose group (mg)	
	0	5
Gross changes n=	6	6
Oral cavity		
Not remarkable	6	0
Alt. content, cheek pouch, unilateral	0	6
Alt. surface, cheek pouch, MF, unilateral	0	4
Discoloration, cheek pouch, proximal, red	0	1
Discoloration, cheek pouch, red, unilateral	0	1
Abscess(es), cheek pouch, focal, unilateral	0	1
Microscopic changes n=	6	6
Oral cavity		
Ulcer, proximal and distal, left		
Mild	0	2
Moderate	0	3
Necrosis, proximal, left		
Minimal	0	1
Inflamm., subacute, prox. & distal, left		
Minimal	0	2
Mild	0	3
Inflamm., neutrophilic, prox. & distal, left		
Minimal	0	1
Mild	0	3
Moderate	0	1
Fibroplasia, cheek pouch, prox. & distal, left		
Minimal	0	2
Mild	0	2

**Summary of individual study findings:** Observations related to mucous membrane irritation were observed in female Syrian hamsters treated with the proposed clinical dose of 5 mg SCH 34117 RediTab with the  formulation. The findings were judged as very slight to severe. Gross findings in the treated group included discoloration, altered surface and abscesses and microscopic findings of minimal to moderate severity included ulceration, necrosis, inflammation and fibroplasia.

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## OVERALL SUMMARY AND EVALUATION:

**Introduction:** The sponsor is developing a rapidly disintegrating desloratadine tablet (RediTab) product for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. The tablets are designed for rapid disintegration in the mouth upon administration to allow ease of swallowing. The sponsor submitted three *in vivo* cheek pouch mucous membrane irritation studies performed in Syrian golden hamsters. In the first study using a \_\_\_\_\_ formulation, the tablets were comprised of SCH 34117, gelatin Type B NF, mannitol USP, aspartame NF, Polacrillin Potassium USP, dye \_\_\_\_\_ red \_\_\_\_\_ tutti frutti flavor \_\_\_\_\_ citric acid USP \_\_\_\_\_ Dosing began with four 5 mg tablets on day 1 followed by two tablets on day 2 and one tablet on the following 3 days. The second study was performed using a \_\_\_\_\_ desloratadine Reditab \_\_\_\_\_ formulation (one 5 mg tablet per day) although the changes to the formulation, if any, were not provided. In the third study, an \_\_\_\_\_ formulation (SCH 34117,

\_\_\_\_\_ ]  
 was utilized (one 5 mg tablet per day). The \_\_\_\_\_ formulation is under development to \_\_\_\_\_ the tablet.

**Safety evaluation:** One death of a SCH 34117-treated animal occurred with the \_\_\_\_\_ formulation in which animals were dosed with 4, 2, and 1 tablet(s) on days 1, 2, and 3, respectively. Cause of death was considered to be due to an interaction with the anesthetic and dosing was 385-1540 times the human dose on a mg/kg basis. Very slight to slight irritation of the hamster cheek pouch was reported in the two studies performed with the \_\_\_\_\_ formulations. These findings either diminished or plateaued with increased dosing. No drug-related gross or microscopic findings were noted in either study. The studies were performed using 5 mg desloratadine tablets which were comparable to those used clinically. The findings of these studies indicate that the SCH 34117 RediTab \_\_\_\_\_ formulations do not pose a significant irritancy risk in the intended population.

In the study performed with the \_\_\_\_\_ formulation (5 mg desloratadine), severe irritation was noted in treated animals as well as gross and microscopic findings (necrosis, ulceration, inflammation and fibroplasia; minimal to moderate severity). The sponsor states that the findings may not be relevant to human risk assessment due to methodological limitations of the assay. The model has historically been used for evaluation of formulations that will have prolonged contact with the oral mucosa, but most specifically has been applied to the evaluation of sublingual tablets intended for local delivery of drug through the oral mucosa. It is an extremely sensitive model since the clinical dose form is applied to the cheek pouch regardless of the animal to human dose ratio. The sponsor explains that the high dose of desloratadine could have resulted in anticholinergic effects that could have affected normal salivary flow. In the clinical setting the action of human salivary flow may have a greater flushing action than would have been operative in hamsters. Residual testing material remained overnight in the cheek pouch indicating that the expected rapid disintegration of the \_\_\_\_\_ tablet was

not operative under the test conditions. The tablet is expected to disintegrate rapidly and be swallowed (based on their experience with \_\_\_\_\_ and residual tablet material in contact with the oral mucosa would not be expected to persist under normal clinical test conditions. Regular flushing action and rapid disintegration would act to reduce residency time and likely remove irritation liability.

Although the sponsor is correct in the historical use of the assay, the claim of a high animal to human dose ratio is not valid since the findings are a local toxicity and are more related to surface area effect than on a body weight effect. The animal dose to human dose ratio is comparable based on buccal mucosa surface area and is equivalent based upon drug concentration at the site of irritation. In addition, a potential toxic effect of desloratadine due to anticholinergic activity on normal salivary flow is not likely since this assay was performed twice using a different formulation but with equivalent or greater daily doses of desloratadine resulting in only very slight to slight irritation.

In regards to the observed toxicity of the \_\_\_\_\_ formulation of the RediTab tablet being a result of residual testing material remaining in the cheek pouch, the Agency currently has no information as to the actual rate of disintegration of this new formulation in clinical studies. \_\_\_\_\_

\_\_\_\_\_ and there is no data to suggest \_\_\_\_\_ based products have irritation liability. However, the \_\_\_\_\_ formulation for desloratadine RediTabs includes \_\_\_\_\_ new components: \_\_\_\_\_

Although none of these new components are expected to have a significant irritation liability individually, the potential exists that the combination of some or all components may produce the observed cheek pouch toxicity.

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**RECOMMENDATIONS:**

Internal comments: [

[

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External recommendations (to sponsor): None at this time.

**Future development or NDA issues:** Should the sponsor pursue development of the \_\_\_\_\_ for RediTab tablets, qualification studies may be necessary for the \_\_\_\_\_ In addition, the sponsor will need to conduct additional preclinical studies to assess the potential for buccal irritation and reversibility of the findings.

Reviewer signature:

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

Team leader signature:

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

Original IND \_\_\_\_\_

CC: HFD-570/Division File  
HFD-570/C.J. Sun  
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/s/

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Timothy McGovern  
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