

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

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

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

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

**Sponsor:** Schering Corporation, Kenilworth, NJ

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

**Class:** Anti-histamine

**Indication:** Seasonal allergic rhinitis

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

**Proposed Clinical Protocols:** None with these submissions.

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

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

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

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

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

Study	Report #	Serial #
<b>Safety Pharmacology:</b>		
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
<b>Pharmacokinetics:</b>		
SCH 34117: A study of the tissue distribution of radioactivity in male and female sprague dawley rats and male 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. 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>

**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.

**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  $\sim$  to  $\sim$   $\mu\text{g equiv/g}$  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	1
Blood	0.875	1.1
Eyes (pigmented)	3.57	4.49
Kidney	9.27	11.7
Liver	26	32.7
Skin (non-pigmented)	1.58	1.99
Skin (pigmented)	1.72	2.16

**Excretion:** Following a single oral dose of  $^{14}\text{C}$ -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%).

## OVERALL SUMMARY AND EVALUATION

**Safety Pharmacology:** SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10  $\mu\text{M}$ ) 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  $\mu\text{M}$ . SCH 34117 also decreased  $V_{\text{max}}$  and velocity of impulse conduction and increased excitation threshold ( $\geq 30 \mu\text{M}$ ) while producing a negative inotropic effect (10  $\mu\text{M}$ ) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100  $\mu\text{M}$ . In isolated rabbit ventricular myocytes, SCH 34117 (100  $\mu\text{M}$ ) reduced  $\text{Na}^+$  current more effectively than 100  $\mu\text{M}$  loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current ( $i_{\text{Kr}}$ ) current to  $\sim 1/2$  control value at  $6 \times 10^{-6} \text{ M}$  as the concentration at which  $1/2$  current is blocked ( $k_{0.5}$ ) was  $5 \times 10^{-6} \text{ M}$  ( $k_{0.5}$  for loratadine was  $8.7 \times 10^{-6}$ ). SCH 34117 had no effect at  $10^{-5} \text{ M}$  on inward rectifier current ( $i_{\text{K1}}$ ) although the curve was flatter at  $3 \times 10^{-5} \text{ M}$ ; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters in vitro at concentrations ranging from  $\sim 1 \mu\text{M}$ . SCH 34117 was previously shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac  $\text{K}^+$  channels as well as a cloned human  $\text{hKv1.5}$ . All findings were observed during in vitro assessments while in vivo studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters. In addition, the absence of loratadine-induced adverse cardiac effects in humans suggests that SCH 34117 is reasonably safe in this regard. A previous consult with Dr. Peter Honig, acting Medical Officer, concluded that no further preclinical assessment of cardiovascular effects is necessary.

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

RECOMMENDATION

None at this time.

Timothy J. McGovern, Ph.D., Pharmacologist

Original IND 55,364

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

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

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

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

**Sponsor:** Schering Corporation, Kenilworth, NJ

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

**Class:** Anti-histamine

**Indication:** Seasonal allergic rhinitis

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

**Related INDs/NDAs:** NDA 21-165

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

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

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

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

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

<u>Study</u>	<u>Report #</u>	<u>Volume</u>
<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 55,364. The review of the addendum which contains recovery data is incorporated with the main study review and can be

found in the Original Review for NDA 21-165. In addition, Study # \_\_\_\_\_  
 \_\_\_\_\_ 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 ICR 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-pentoxoresorufin 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.

**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.

**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
<b>Enzyme Induction</b>										
% 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
I. EROD										
pmol/min/mg micros. protein		↑180	↑150	↑312	↑992		↑58	↑90	↑160	↑233
pmol/min/g liver		↑160	↑151	↑439	↑1298		↑81	↑134	↑212	↑526
pmol/min/total liver		↑181	↑173	↑542	↑1715		↑90	↑154	↑526	↑603

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

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

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

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

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

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

AOW: Absolute organ weight

RTB: Relative to body weight

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

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

Observation	Males					Females				
	0	24	48	96	192	0	24	48	96	192
Dose (mg/kg)										
n =	10	10	10	10	10	10	10	10	10	10
Stomach – altered content, black	0	0	0	0	1	0	0	0	0	0
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.

**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										

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	0	5
Moderate						0	0	0	0	5
Vacuolation, corp lutea										
Minimal						0	0	0	0	1
Mild						0	0	0	0	2
Moderate						0	0	0	0	6
Necrosis, granulosa cell										
Minimal						0	0	0	0	4
Mild						0	0	0	0	3
Moderate						0	0	0	0	2
Pancreas	10	0	0	10	10	10	0	0	10	10
Vacuolation, epithelium exocrine										
Minimal	0			0	2	0			0	2
Mild	0			0	8	0			0	8
Parathyroid glands	10	0	7	7	10	10	0	9	10	10
Vacuolation, chief cell										
Minimal	0		0	0	2	0		0	0	0
Pituitary gland	10	0	10	9	10	10	0	9	10	10
Vacuolation, pars anterior										
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	10	0	0	10	10	10	0	0	10	10
Vacuolation, ductular										
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	10	1	0	10	10					
Vacuolation, epithelium										
Mild	0	0		0	10					
Skeletal muscle	10	0	0	10	10	10	0	0	10	10
Vacuolation, myofiber										
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	10	10	10	10	10	10	10	10	10	10
Vacuolation, epithelium										
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,										

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

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

<b>Histopathology</b>	<b>Males</b>					<b>Females</b>				
<b>Dose group (mg/kg)</b>	0	24	48	96	192	0	24	48	96	192
Minimal						0			0	1
Mild						0			0	2
Moderate						0			0	1

**APPEARS THIS WAY  
ON ORIGINAL**

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  $\pm$  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 ( $\mu$ g/plate)	Positive Controls With S9 ( $\mu$ g/plate)
TA 1535	sodium azide (5)	2-aminoanthracene (2.5)
TA 97a	9-aminoacridine (75)	2-aminoanthracene (2.5)
TA 98	2-Nitrofluorene (5)	2-aminoanthracene (2.5)
TA 100	sodium azide (5)	2-aminoanthracene (2.5)
TA 102	Cumene hydroperoxide (200)	2-aminoanthracene (5)
WP2 uvrA	N-Ethyl-N'-nitro-N-nitrosoguanidine (2)	2-aminoanthracene (20)

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

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

The experiments were performed using triplicate plates at each concentration incubated for 48 hours  $\pm$  S9. Cytotoxicity was evaluated based on a reduction in revertant colony counts by  $\sim$  30%, inhibition of background bacterial lawn growth and “additional factors based on scientific judgment”. Tests were valid if overnight bacterial cultures reached a density of at least  $5 \times 10^8$  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 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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Timothy J. McGovern, Ph.D., Pharmacologist

Addendum 1: Histopathology inventory for SCH 34117.

IND 55,364

CC:

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

**Addendum 1: Histopathology inventory for IND 55,364.**

\* Organ weight obtained

Study No.	P-6526	D18289	SN 98088	P-6973	P-6527	SN 98089	P-6976	SN 97253
Duration	14-day	14-day	28-day	3-month	14-day	28-day	3-month	3-month
Species	rat	rat	rat	Rat	monkey	monkey	monkey	mouse
Adrenals	X*		X*	X*	X*	X*	X*	X
Aorta	X		X	X	X	X	X	X
Bone marrow smear	X		X	X	X	X	X	X
Bone (femur)	X		X	X	X	X	X	X
Bone (rib)					X	X		
Bone (strenum)	X		X		X	X		
Brain:	X*		X*	X*	X*	X*	X*	X*
Cecum	X		X		X	X		
Cervix			X					
Colon	X		X		X	X		
Duodenum	X		X	X	X	X	X	
Epididymis	X*		X*	X*	X*	X	X*	X*
Esophagus	X		X	X	X	X	X	X
Eye	X		X	X	X	X	X	X
Fallopian tube								
Fat								
Gall bladder					X	X	X	X
Gross lesions	X	X			X	X	X	X
Harderian gland	X		X	X				X
Heart	X*		X*	X*	X*	X*	X*	X*
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

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

**NDA No.** 21-165 **Submission Date:** 04 OCT 2000

**Reviewer:** Timothy J. McGovern, Ph.D. **Review Completed:** 19 OCT 2000

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

**Sponsor:** Schering Plough Corp.

**Drug Names:** CLARINEX **Code Name:** Descarboethoxyloratadine

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

**LABELING REVIEW:**

In the section entitled "Clinical Pharmacology", the sponsor proposes that the phrase ~~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~~ 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~~

7 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

RECOMMENDATIONS

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

---

Timothy J. McGovern, Ph.D., Pharmacologist

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

Studies	DCL AUC	DCL + DCL metabolites AUC	Animal:human ratio	PB correction	derivation of animal AUC
Human - 5 mg	56.9	711.25			
rat: fertility					
3 mg/kg	1950	8863.64	12	8	3 mos tox study, males
12mg/kg	10440	47454.55	67	44	40% of 30 mg/kg dose in 3 mos study, males
24 mg/kg	31606	143663.64	202	134	Embryo-fetal rat study
rat: embryo fetal					
6 mg/kg	7875	35795.45	50	33	Embryo-fetal rat study
24 mg/kg	31606	143663.64	202	134	Embryo-fetal rat study
48 mg/kg	49238	223809.09	315	208	Embryo-fetal rat study
rat: Seg III					
3 mg/kg	1619	7359.09	10	7	1 month rat tox study
9	10999	49995.45	70	47	30% of 30 mg/kg dose in 1 month tox study
18	21998	99990.91	141	93	60% of 30 mg/kg dose in 1 month tox study
rabbit: embryo-fetal					
60 mg/kg	12987	NA	228	NA	Embryo-fetal rabbit study
Overdosage					
rat-250 mg/kg	27441	124731.82	175	116	1-week Pk study at 240 mg/kg; M+F
Carcinogenicity					
Mouse - 40 mg/kg	1861	5029.73	7	3	28-day dietary study w/fortadine
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/fortadine
Rat - 10 mg/kg	1619	7359.09	10	7	28-day dietary study w/fortadine
QTc:					
Monkey - 24 mg/kg	54346	NA	955		3-mos monkey (P6976) at 24 mg/kg
Species	DCL/14C ratio	Protein binding (%)			
Mouse	0.37	94.4			
Rat	0.22	90.5			
Human	0.08	85.6			
Monkey	NA	85.8			

Drug: **Clarinet**

		# daily							
	age	mg/dose	doses	mg/day	kg	mg/kg	factor	mg/m <sup>2</sup>	
Pediatric				0	3	0.00	25	0.00	
Adult	>12	5	1	5	50	0.10	37	3.70	
		conv.		Dose Ratio		Rounded Dose Ratio			
	route	mg/kg/d	factor	mg/m <sup>2</sup>	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			---	---	---	---	---	---

**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 desloratadine-induced inhibition of various cellular mediators in vitro 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 antihistamine 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.

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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

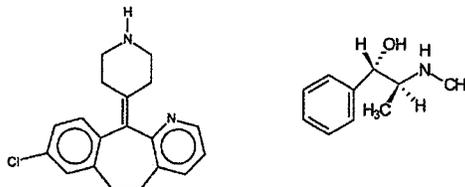
HFD-590/K. Hastings

**REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA**  
Original Review

**KEY WORDS:** extended release, reformulation, combination product  
**Reviewer Name:** W. Mark Vogel, Ph.D.  
**Division Name:** Division of Pulmonary Drug Products  
**HFD#:** HFD-570  
**Review Completion Date:** September 15, 1999  
**IND Number:** 58,506  
**Serial Number:** 000  
**Submission Dates:** June 18, 1999  
**Submission Type:** Original IND  
**Information to Sponsor:** Yes (✓), No ( )  
**Sponsor or Agent:** Schering, Corporation, Kenilworth, NJ

**Drug Name:** SCH 483 -BID is the designation for a combination tablet containing:  
**Generic Name:** Descarboethoxy loratadine (DCL) Pseudoephedrine sulfate (PSE)  
**Alternate Name:** Desloratadine N/A  
**Code Name:** SCH 34117 N/A  
**Chemical Name:** 5H-benzo [5,6]cyclohepta[1,2-b] pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene) benzenemethanol, α-[1-(methyl amino) ethyl]-, [S-(R\*,R\*)]- sulfate (2:1) salt  
**Molecular Formula:** C<sub>19</sub>H<sub>18</sub>ClN<sub>2</sub> (C<sub>10</sub>H<sub>15</sub>NO)<sub>2</sub> • H<sub>2</sub>SO<sub>4</sub>  
**Molecular Weight:** 310.82  
**Drug Class:** antihistamine sympathomimetic  
**Dosage:** ----- one tablet twice daily -----  
**Content (mg/tablet):** 2.5 120  
**Dose (mg/day):** 5 240

**Structures:**



**Relevant INDs/NDAs/DMFs:**

IND	oratadine tablet	IND 58,545	Desloratadine PSE once daily tablet
IND	Loratadine PSE tablet	NDA 19-658	Claritin (Loratadine tablet)
IND 55,364	Desloratadine tablet	NDA 19-670	Claritin-D 12 Hr (Loratadine PSE)
IND 57,960	Desloratadine syrup	NDA 20-470	Claritin-D 24 Hr (Loratadine PSE)

**Indication:** Allergic rhinitis and chronic idiopathic urticaria

**Route of Administration:** Oral

**Clinical Formulation (and components):** tablet with immediate release formulation of desloratadine and extended release formulation of pseudoephedrine:

Ingredient	mg/tablet	Function
1. Desloratadine (DCL) Immediate Release Layer:		
2. Pseudoephedrine (PSE) Sustained Release Layer:		
Nominal Tablet Weight		

**Proposed Clinical Studies:**

A protocol was submitted only for the first study listed below.

Study:	Subjects:	Treatment:	No. subjects
Open label, bioequivalence 3-way cross-over	Healthy adult volunteers	Single Dose SCH-483 vs individual DCL and PSE	36
2-way crossover food effect PK study	Healthy adult volunteers	Single dose SCH-483 in fasted vs fed subjects	24
Steady state PK study	Healthy adult volunteers	SCH-483 BID × 14 days	18
Safety and efficacy	Allergic rhinitis patients	SCH-483 BID vs 5 mg DCL QD + 120 mg PSE BID × 14 days	600
Safety and efficacy	Allergic rhinitis patients	Same as above	600

**Previous Reviews, Dates and Reviewers:** There are no previous reviews under this IND. Relevant background reviews of other submissions are listed on the following page.

Submission:	Submission Date:	Reviewer:	Review Date:
Desloratadine (DCL) Original IND 55,364	03/09/98	T. McGovern	03/22/98
DCL 1-month rat and monkey toxicity	07/29/98	T. McGovern	10/27/98
DCL 3-mo monkey summary	11/23/98	T. McGovern	12/15/98
Loratadine Syrup Original NDA 20-641	10/13/95	M. Vogel	09/04/96
Loratadine Tablet Original NDA 19-658	10/31/86	B.C.Y. Tai	10/30/87

**Studies Reviewed within this Submission:** } No new preclinical studies sub-  
**Studies Not Reviewed within this Submission:** } mitted to this IND; cross-  
**Studies Previously Reviewed:** } referenced to IND 55,364

*Note: Portions of this review may be excerpted directly from the sponsor's submission.*

**Introduction/Drug History:** Desloratadine (SCH 34117) is the active metabolite of loratadine. Desloratadine has antihistamine potency 1-20 times that of the parent loratadine depending on species and model. Desloratadine has weak antimuscarinic activity that the parent loratadine does not exhibit in vitro. The toxicity profile of loratadine is due primarily to systemic phospholipidosis that, with increasing dose and duration, ultimately affects virtually every organ system. The tissues most sensitive to phospholipidosis are: lung macrophages, peripheral lymphocytes, liver, kidney, lymphoid organs, male and female reproductive organs, endocrine and exocrine glands. The ratio for steady-state plasma AUC of desloratadine/loratadine in humans given the recommended daily dose of 10 mg is about 4:1. Loratadine is a widely used antihistamine, first approved by FDA in 1993. A pediatric syrup and a rapidly disintegrating loratadine tablet formulation are also approved. The combination of loratadine plus pseudoephedrine is approved in a BID and once daily formulation.

IND 55,364 for a tablet form of desloratadine was submitted 09 March 1998. Single dose PK data from adults (2.5-20 mg) in non-US studies were submitted to IND 55,364. No new preclinical data were submitted to support the present IND; all of the preclinical data submitted to IND 55,364 are cross-referenced to the present IND. A separate IND for a once a day formulation of desloratadine plus pseudoephedrine was submitted (IND 58,545, June 25, 1999); that IND also cited IND 55,364 for supporting preclinical studies. Preclinical studies submitted to or cited in IND 55,364 and reviewed to date include: histamine receptor binding and antihistaminic efficacy studies, effects on cardiac K<sup>+</sup> channels, comparative CNS and cardiovascular profiles, metabolic profiling in rat, mouse and monkey, acute toxicology in mice, rats, and monkeys, 14-day and 28-day multiple-dose toxicity studies in rats and monkeys, bacterial mutation and in vitro chromosome genetic toxicity assays, pilot (dose-ranging) reproductive toxicity studies in rats and rabbits. A report of a 3-month multiple dose monkey toxicity study is submitted but has not yet been reviewed.

**Previous Clinical Experience:** There is no human clinical experience with the SCH-483

combination. One phase-2 placebo-controlled study, and three phase-3 placebo-controlled studies of desloratadine in seasonal allergic rhinitis have been completed with durations of 2-4 weeks. The bioavailability of pseudoephedrine alone from a prototype of the SCH 483 formulation has been determined in a human study. Safety and tolerance of desloratadine tablets was also assessed in rising single-dose (2.5-20 mg) and multiple-dose (5-20 mg/kg) studies. There is substantial clinical exposure to pseudoephedrine in the presence of desloratadine as a metabolite of loratadine in the marketed Claritin-D products (BID and QD formulations).

#### OVERALL SUMMARY AND EVALUATION:

No nonclinical toxicology data was submitted with this IND; all nonclinical supporting data are by cross reference to IND 55,364 for desloratadine tablets. The data submitted to IND 55,364 should be sufficient to support the safe use of desloratadine if:

- The recently submitted 3-month toxicity study in monkeys confirms that desloratadine has a similar toxicological profile as loratadine and an adequate NOAEL has been defined,
- The CDER Carcinogenicity Assessment Committee concurs that exposure to desloratadine in previous rodent carcinogenicity studies of parent loratadine is sufficient to support desloratadine products,
- There are no biologically significant differences between the metabolite profiles observed after oral administration of loratadine or desloratadine.

There is no established Center-wide policy on the need for animal studies to support combination products. The practice in some divisions has been that no additional animal studies are needed to support the combination of two already marketed products. The combination of desloratadine with pseudoephedrine does not strictly fit this scenario because desloratadine itself is not presently approved for marketing. However, there is substantial clinical experience with combined exposure to pseudoephedrine and desloratadine as a metabolite of loratadine in the marketed Claritin-D products. The systemic exposure to desloratadine from the SCH-483 combination product is anticipated to be similar to that from existing loratadine formulations. A bridging toxicology program is being conducted for desloratadine alone to relate the toxicology of that moiety to the extensive toxicological base for loratadine. Since desloratadine is not a marketed product, it is recommended that the desloratadine/pseudoephedrine combination should be tested in a bridging general toxicity study in one species for up to 90 days and in a teratology study in one species. It is recommended that these studies be conducted during IND development for registration of the combination product. Additional animal studies of desloratadine alone might be needed before marketing of any desloratadine product if the conditions outlined above are not met.

**Formulation Issues:** All of the excipients are standard compendial agents. Under 2-weeks accelerated stability conditions only one degradation product of pseudoephedrine

was detected at the level of 0.03%. Several unknown degradation products of desloratadine were observed with none above 0.13%. Impurity issues will need to be revisited when additional stability data are available. Drug substance is from the same source as in IND 57,960; the Division has agreed that drug substance stability issues will be addressed under that IND.

#### RECOMMENDATIONS

1. Based on preclinical studies with desloratadine alone and previous clinical experience with desloratadine, loratadine, and the combination of loratadine plus pseudoephedrine, it is safe to proceed with the proposed clinical studies of the desloratadine-pseudoephedrine combination, SCH 483, BID.
2. Since desloratadine is not a marketed product, it is recommended that the desloratadine/pseudoephedrine combination be tested in a bridging general toxicity study in one species for up to 90 days and in a teratology study in one species. It is recommended that these studies be conducted during IND development for registration of the combination product.

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Mark Vogel, Ph.D., Pharmacologist

Original IND 58,506  
c.c. HFD-570/Division File  
HFD-570/C.J. Sun  
HFD-570/W.M. Vogel  
HFD-570/G. Trout

## PHARMACOLOGY/TOXICOLOGY COVER SHEET

IND number: 58,506

Review number: 2

Sequence number/date/type of submission:

016/May 26, 2000/IT

023/November 21, 2000/IT

Information to sponsor: Yes ( ) No (✓)

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

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

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

Division name: Pulmonary and Allergy Drug Products

HFD#: 570

Review Completed: 23 OCT 2001

**Drug:**

Trade Name: CLARINEX-D 12 Hour Extended Release Tablet

Generic: Descarboethoxyloratadine (DCL)/pseudoephedrine sulfate (PSE)

Code Name: SCH 483

Chemical name:

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

$\alpha$ -[1-(methylamino) ethyl]-[S-(R\*,R\*)]-benzenemethanol sulfate (2:1) (salt)

CAS registry number: NA

Mole file number: NA

Molecular formula/molecular weight:

DCL: C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>/310.8

PSE: (C<sub>10</sub>H<sub>15</sub>NO)<sub>2</sub>H<sub>2</sub>SO<sub>4</sub> —

**Structure:**

Desloratadine:	
Pseudoephedrine:	

**Relevant INDs/NDAs/DMFs:**

IND 55,364 Descarboethoxyloratadine tablets

IND 58,506 SCH 483-BID tablet

NDA 21-165 Clarinex (Seasonal allergic rhinitis)

NDA 21-297 Clarinex (chronic idiopathic urticaria)

NDA 21-300 Clarinex Syrup (Seasonal allergic rhinitis and chronic idiopathic urticaria)

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



## PHARMACOLOGY/TOXICOLOGY REVIEW

### I. PHARMACOKINETICS/TOXICOKINETICS:

**Metabolism:** The study "Identification of Desloratadine D12 Tablet degradants ( \_\_\_\_\_ and \_\_\_\_\_, as *In Vivo* and *In Vitro* rat metabolites" was submitted in submission 023. Male Sprague Dawley rats were administered oral doses of 6.5 mg/kg with a suspension of <sup>14</sup>C-SCH 34117 in 0.4% methylcellulose. Plasma samples after 3 hours revealed the presence of the degradants \_\_\_\_\_ and \_\_\_\_\_ while none was detected in urine samples (0-24 hours). *In vitro* incubations of <sup>14</sup>C-SCH 34117 with \_\_\_\_\_-treated rat liver microsomes of S9 fractions performed with 1 nmol P-450/ml at drug concentrations of 35 and 100 μM also demonstrated the presence of \_\_\_\_\_ was also detected in liver S9-fraction samples. The sponsor concludes that these findings suggest that male Sprague Dawley rats dosed orally with SCH 34117 would have been exposed to significant levels of \_\_\_\_\_ equivalents in the form of \_\_\_\_\_ and \_\_\_\_\_. In addition, bacterial mutagenicity and \_\_\_\_\_ assays using SCH 34117 preincubated with \_\_\_\_\_-treated rat liver S9 fraction would reflect exposure to both \_\_\_\_\_ and \_\_\_\_\_.

**PK/TK summary:** The Desloratadine D12 Tablet degradants \_\_\_\_\_ and \_\_\_\_\_ were detected in male rat plasma 3 hours following oral administration of 6.5 mg <sup>14</sup>C-SCH 34117/kg. None was detected in urine samples. *In vitro* incubations of <sup>14</sup>C-SCH 34117 with \_\_\_\_\_-treated rat liver microsomes of S9 fractions at drug concentrations of 35 and 100 μM also demonstrated the presence of \_\_\_\_\_ was also detected in liver S9-fraction samples.

**PK/TK conclusions:** Male Sprague Dawley rats dosed orally with SCH 34117 are likely exposed to \_\_\_\_\_ equivalents in the form of \_\_\_\_\_. In addition, assays using SCH 34117 preincubated with \_\_\_\_\_-treated rat liver S9 fraction would reflect some exposure to both \_\_\_\_\_.

### II. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

**Study title:** Dose-range finding and pilot embryo-fetal developmental toxicity study of SCH 483 administered by oral gavage in rabbits.

**Key study findings:** No mortality, clinical signs body weight changes or changes in food consumption were noted in nonpregnant female rabbits administered six daily doses of SCH 34117 and psuedoephedrine sulfate at doses up to 9.6 and 460.8 mg/kg/day, respectively. No other parameters were evaluated; the study was terminated as an internal memo was included in the report and stated that, based on conversations with the FDA, toxicology studies with SCH 483 will not be required if the NDA is intended for submission after approval of the DCL NDA. It should be noted that the NDA for SCH 483 was submitted prior to approval of the original DCL NDA (NDA 21-165).

**Study no.:** 97302

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

**Conducting laboratory and location:** Safety Evaluation Center, Schering Plough Research Institute, Lafayette, NJ

**Date of study initiation:** 11/4/1999

**GLP compliance:** No.

**QA reports:** yes ( ) no (✓)

**Drug, lot #, radiolabel, and % purity:**

SCH 34117: IRQ-99-19M1, NA, \_\_\_\_\_

SCH 4855, Pseudoephedrine sulfate: MI-B-06155, NA, \_\_\_\_\_

**Formulation/vehicle:** 0.4% aqueous methylcellulose

**Methods:**

Species/strain: New Zealand white rabbit (Hra:[NZW]SPF)

Doses employed:

Group	Test/Control Article	Total daily dose (mg/kg)	Dose volume (ml/kg)	Dose conc. (mg/ml)
6	Veh. Control	0	4	0
7	SCH 4855 Control: Methylcellulose	0	2	0
	SCH 4855	460.8	2	230.4
8	SCH 483:			
	SCH 34117	1.2	2	0.6
	SCH 4855	57.6	2	28.8
9	SCH 483:			
	SCH 34117	2.4	2	1.2
	SCH 4855	115.2	2	57.6
10	SCH 483:			
	SCH 34117	4.8	2	2.4
	SCH 4855	230.4	2	115.2
11	SCH 483:			
	SCH 34117	9.6	2	4.8
	SCH 4855	460.8	2	230.4

Route of administration: oral gavage

Study design: Study consisted of 2 phases: First phase: Assess toxicity of SCH 483 by oral gavage to nonpregnant rabbits (4-5 mos of age, 2.75-3.37 kg). Animals were dosed daily on study days 0-5. Second phase: Assess potential maternal and embryo-fetal toxicity of SCH 483 when administered by oral gavage to pregnant rabbits during the period of organogenesis. Study was terminated prior to completion of Phase 1 and initiation of Phase 2.

Number/sex/group: 2 nonpregnant females per dose group

Parameters and endpoints evaluated: viability, clinical observations, body weight, food consumption, hematology and serum chemistry. No necropsy was performed.

**Results:**

Mortality: No mortality was observed in any dose group.  
Clinical signs: No remarkable clinical observations noted.  
Body weight: No significant findings noted.  
Food consumption: No changes were noted.  
Hematology and serum chemistry: No results reported.  
Toxicokinetics: Not assessed.

**Summary of individual study findings:** No mortality, clinical signs body weight changes or changes in food consumption were noted in nonpregnant female rabbits administered six daily doses of SCH 34117 and pseudoephedrine sulfate at doses up to 9.6 and 460.8 mg/kg/day, respectively. No other parameters were evaluated as the study was terminated as an internal memo was included in the report and stated that, based on conversations with the FDA, toxicology studies with SCH 483 will not be required if the NDA is intended for submission after approval of the DCL NDA. It should be noted that the NDA for SCH 483 was submitted prior to approval of the original DCL NDA (NDA 21-165).

**Reproductive and developmental toxicology summary:** No complete studies have been performed with the combination of SCH 34117 and pseudoephedrine sulfate.

**Reproductive and developmental toxicology conclusions:** No conclusions can be determined from the above study.

**Labeling recommendations:** The label for the drug product should reflect that for SCH 34117, namely a pregnancy label of "C".

**III. DETAILED CONCLUSIONS AND RECOMMENDATIONS:**

**Conclusions:** The submitted metabolism study shows that male Sprague Dawley rats dosed orally with SCH 34117 are likely exposed to \_\_\_\_\_ equivalents in the form of \_\_\_\_\_ and \_\_\_\_\_. In addition, assays using SCH 34117 preincubated with \_\_\_\_\_-treated rat liver S9 fraction would reflect some exposure to both \_\_\_\_\_ and \_\_\_\_\_. Although the sponsor's conclusion that bacterial mutagenicity and HPBL clastogenicity assays using SCH 34117 preincubated with \_\_\_\_\_-treated rat liver S9 fraction would reflect exposure to both \_\_\_\_\_ and \_\_\_\_\_, these studies would not be expected to adequately assess the genotoxic potential of the degradants since testing in these assays in the presence of a structural alert should utilize the limit doses for the assays for each compound tested. The submitted dose-range finding and pilot embryo-fetal developmental toxicity study of SCH 483 in rabbits provides no useful information since the study was terminated prior to completion.

**General Toxicology Issues:** The safe use of PSE in humans has been determined previously with substantial clinical exposure to PSE in the presence of SCH 34117 as a metabolite of loratadine in the marketed Claritin-D products (BID and QD formulations). However, since SCH 34117 is not a currently marketed product, Dr. Mark Vogel recommended that the desloratadine/PSE combination should be tested in a bridging general toxicity study in one

species for up to 90 days and in a teratology study in one species during IND development for registration of the combination product (see Original IND review dated September 15, 1999). The sponsor was later informed that these studies would not be necessary if the NDA for the desloratadine/PSE combination product was submitted after approval of the NDA for desloratdine tablets (NDA 21-165). It should be noted that the NDA for the combination (NDA 21-313) was submitted in December of 2000, prior to approval of NDA 21-165. The above-recommended studies are still deemed unnecessary as long as NDA 21-165 is approved prior to the time for an approval decision for NDA 21-313.

**Recommendations:** None at this time.

Reviewer signature:

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

Supervisor signature: Concurrence -

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

IND 58,506

cc: list: C.J. Sun  
T.J. McGovern

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

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Timothy McGovern  
10/23/01 05:39:20 PM  
PHARMACOLOGIST

Joseph Sun  
10/25/01 09:47:00 AM  
PHARMACOLOGIST  
I concur.