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

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

Results:

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

Clinical Observations: No drug-related effects were noted.

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

Table 27: Summary of effects on body weight gain.

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

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

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

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

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

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

Table 29: Summary of histopathologic findings in male rats.

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

Severe	0	0	4	15	6
Hyperplasia					
Minimal	0	0	0	7	3
Mild	0	0	0	0	4
Pituitary gland					
Vacuolation – cytoplasmic, Rathke's Pouch, macrophage					
Minimal	2			11	3

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

Table 30: Summary of spermatogenic endpoints.

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

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

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

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

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

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

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

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

Shaded area indicates statistically significant difference from control value.

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

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

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

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

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

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

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

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

Dams:

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

Fetuses (F_1):

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

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

Results:

Dams:

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

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

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

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

Necropsy: No drug-related effects were noted.

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

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

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

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

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

Fetuses (F1):

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

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

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

Shaded area indicates statistically significant difference from control value.

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

Oral embryo-fetal development study of SCH 34117 in rabbits
Report No.: P-6802 *Study No.*: 97116 *Volume*: 1.32

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

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

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

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

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

Dams:

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

Fetuses (F_1):

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

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

Results:

Dams:

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

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

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

Necropsy: No drug-related findings were observed.

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

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

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

Shaded area indicates statistically significant difference from control value.

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

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

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

Fetuses:

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

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

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

Oral peri- and post-natal development study of SCH 34117 in rats
Study No.: 97117 *Volume*: 1.33

Study Dates:	Starting date 1/9/1998; report issued 5/23/1999
Testing Lab:	Safety Evaluation Center, Schering Plough Research Institute, Lafayette, NJ
Test Article:	SCH 34117 (Batch# 97-34117-X-02 RA; purity = 99%) in 0.4% aqueous methylcellulose
Concentration:	0.6-3.6 mg SCH 34117/ml
Dose Volume:	5 ml/kg/day
GLP:	The study was accompanied by a signed GLP statement.
QA report:	Yes.

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

Methods: Mated female rats (12 weeks old; 231-322 g) were assigned to the following treatment groups:

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

Female rats (F_0) were placed with males (1:1) for mating until positive evidence of mating was found. The day of mating was designated as Day 0. Mated females received a daily dose of vehicle or test drug by esophageal intubation once a day during the peri-natal (day 6 of gestation) and lactation periods (day 21 postpartum). On day 4 postpartum, the number of offspring per litter was adjusted by randomly selecting 4 male and 4 female offspring, keeping 8 offspring alive when 4 of each sex were not available. No adjustment was made when the number of offspring per litter was less than 8. On day 21 postpartum, one male and female were randomly selected from each litter for postweaning behavioral and developmental measurements, and for later breeding to produce a F_2 generation. The following observations were made:

Dams:

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

F_0 parturition . . . . . Assessment for abnormal labor, nursing, or nesting behavior, length of gestation.

Necropsy . . . . . Lactation day 21, examined for external and visceral changes and implantation sites.

Offspring (F_1):

Litter size . . . . . number of live and dead offspring recorded daily until lactation Day 21. Survival rate calculated for lactation Days 0, 1-4 and 5-21.

Sex determination . . . . . pups sexed externally on lactation days 0, 4, and 21

Clinical observation . . . daily from lactation days 0-21

Body weight . . . . . Days 0, 4, 7, 14, and 21 postpartum; weaned F_1 rats weighed weekly until mating, after mating F_1 females weighed on pregnancy Days 0, 6, 9, 12, 15, 18 and 21, and on lactation days 1 and 4.

Maturational and Behavioral Evaluations

Surface righting test: lactation day 5 through 12
Auditory startle test: lactation day 10 through 15
Eye opening: lactation day 12 through 16
Incisor eruption: lactation day 9 through 14
Negative geotaxis test: lactation day 6 through 10
Open field test: lactation days 15, 16 and 17

Gross visceral exam . . . animals not selected for post-weaning measurements and breeding sacrificed on day 21 of lactation and subjected to gross visceral examination

F1 post-weaning measurements . . . one male and female from each litter: body weights measured weekly, observed daily from post-partum day 22 through sacrifice, F_1 females checked for vaginal opening form Day 29 through Day 35 postpartum, F_1 males checked for preputial separation from postpartum day 39 through day 50.

F_1 estrus cycle determination . . . evaluated from 1 week prior to mating and during mating period by vaginal cytology

F_1 mating . . . . . at 11-12 weeks of age, one male from each litter was placed with a female from a different litter within the same dose group for up to 2 weeks. Female was separated once mating occurred. Unmated females paired for up to one more week with a proven male from same dose group.

Offspring (F2):

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

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

Results:

Dams:

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

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

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

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

Table 37: Summary of effects on clinical findings.

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

Shaded area indicates statistically significant difference from control value.

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

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

Offspring (F_1):

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

Table 38: Effect of SCH 34117 on pup survival.

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

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

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

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

Table 39: Summary of effects on F_1 clinical findings.

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

Shaded area indicates statistically significant difference from control value.

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

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

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

Necropsy: No SCH 34117-related gross external and visceral findings were observed in culled and dead F_1 pups or F_1 adults.

Offspring (F2):
No significant differences were noted in body weight on days 0 or 4. Pup survival was reduced at the high-dose (92.9% vs 97.5% in controls) although the finding was not significant. There were no SCH 34117-related gross external or visceral observations.

Key study observations: The NOAEL for developmental toxicity of the F_1 pups was 3 mg/kg due to reduced body weight gain and fetal development effects. A NOAEL of > 18 mg/kg was selected for reproductive indices of the first generation offspring and development of the second generation offspring. A NOAEL of 9 mg/kg was observed for the F_0 dams due to reduced body weight gain and food consumption at the high dose.

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

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

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

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

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

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

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

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

OVERALL SUMMARY AND EVALUATION:

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

Pharmacodynamics: SCH 34117 demonstrated a high selectivity for H_1-receptors over H_2 or H_3-receptors and displayed a 14-fold greater affinity for the H_1-receptor than loratadine in cloned H_1 human receptor subtypes (IC_{50} = 51 and 721 nM, respectively). This finding was confirmed in isolated guinea pig lung tissue (IC_{50} = 840 and 3030 nM for SCH 34117 and loratadine, respectively). SCH 34117 was also ~ 18-fold more potent than loratadine in rat brain H_1-receptor activity (SCH 34117 K_i = 4.8-7 nM) and was comparable in potency to its primary unconjugated metabolites. In an *in vitro* assessment of antihistaminic activity using guinea pig isolated ileum, SCH 34117 was up to 20-fold more potent than loratadine and was 4 to 8.5-fold more potent in inhibiting histamine-induced bronchospasm *in vivo* (SCH 34117 ED_{50} = 0.11-0.27 mg/kg, IV). *In vivo* studies performed for the loratadine program demonstrated that SCH 34117 was 2.5-4 times more potent than loratadine following oral administration in mice and guinea pigs. SCH 34117 also expressed a high affinity for cloned human M_1 and M_3 receptor subtypes (IC_{50} = 48 and 125 nM). In a separate study, SCH 34117 showed greatest activity at central H_1 receptors (IC_{50} = 17 nM) while activity at peripheral H_1 receptors was similar to that at M_2 muscarinic receptors (IC_{50} = 131-168 nM). Other receptor sites tested showed significantly reduced activity. Thus, the results in the Clinical Pharmacology of the labeling submitted by the sponsor concerning the increased relative potency of SCH 34117 compared to loratadine are acceptable.

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

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

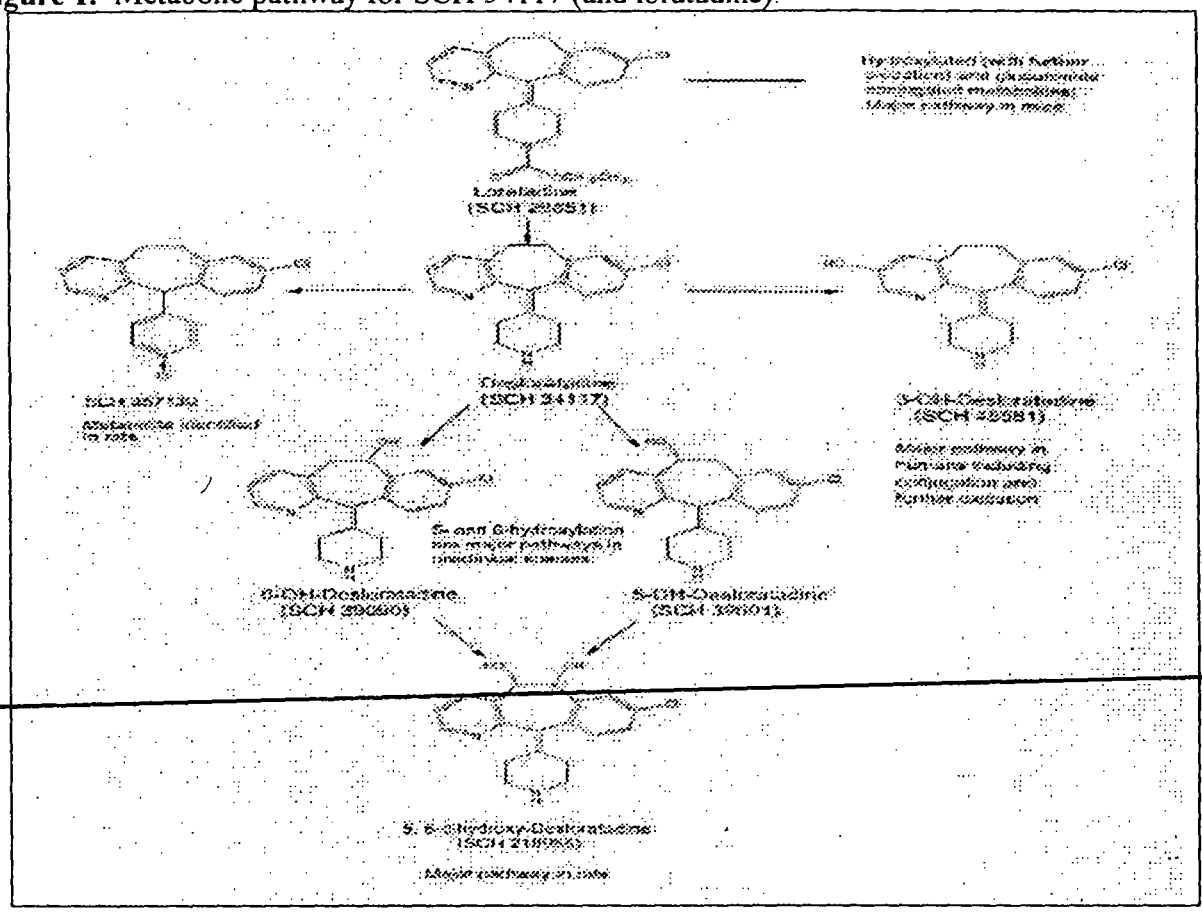
Safety Pharmacology: In vivo assessments of SCH 34117-related effects on cardiovascular function demonstrated that no significant in vivo cardiovascular effects were observed in rats or monkeys (doses up to 12 mg/kg, oral, or 10 mg/kg, intraperitoneal) or in guinea pigs (25 mg/kg SCH 34117, IV). In a study cited by the sponsor[1], loratadine (30 and 100 mg/kg, IV) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 μg/ml), in contrast to terfenadine, quinidine and diphenhydramine which induced significant cardiovascular and ECG effects. Resulting SCH 34117 concentrations (1.46 μg/ml) were 370-fold greater than its C_{max} in man after a single oral dose of 10 mg loratadine.In vitro studies showed that SCH 34117 and loratadine were significantly less potent than terfenadine in inhibiting rat ventricular myocyte and guinea pig cardiac K^+ channels. SCH 34117 did exert effects on various cardiac parameters in vitro at concentrations ranging from 5-100 μM. SCH 34117 blocked hKv1.5 channels cloned from human ventricle and expressed in a mouse cell line (Ltk-), in a concentration-, voltage-, and time-dependent manner. SCH 34117 (1 to 100 μM) also inhibited a cloned human hKv1.5 current with an K_D of 12.5 μM, but was less potent than loratadine or terfenadine (K_D=1.0 and 0.8 μM, respectively). Thus, the relative potency is terfenadine > loratadine > SCH 34117. SCH 34117 was ~ 7-fold less potent than loratadine in blocking KV1.5 channel in HEK 293 cells and loratadine (10 μM) failed to significantly alter HERG currents. Both drugs (up to μM) had minimal effects on I_{HERG} current (15-20%) compared to terfenadine and quinidine (IC50 = 82 and 168 nM, respectively). SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10 μM) in isolated rabbit hearts, due primarily to increasing the QRS complex up to 5-6-fold. SCH 34117 did not increase JT interval alone but enhanced a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50 μM. SCH 34117 also decreased Vmax and velocity of impulse conduction and increased excitation threshold (≥ 30 μM) while producing a negative inotropic effect (10 μM) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100 μM. In isolated rabbit ventricular myocytes, SCH 34117 (100 μM) reduced Na+ current more effectively than 100 μM loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) current to ~ ½ control value at 6×10^{-6} M as the concentration at which ½ current is blocked (k0.5) was 5×10^{-6} M (k0.5 for loratadine was 8.7×10^{-6}). SCH 34117 had no effect at 10^{-5} M on inward rectifier current (iK1) although the curve was flatter at 3×10^{-5} M; loratadine had more pronounced effect than SCH 34117. Since SCH 34117 has been shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K+ channels as well as a cloned human hKv1.5, all findings were observed during in vitro assessments while in vivo studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters, and loratadine-induced cardiac effects have not been observed in humans, SCH 34117 is considered to be reasonably safe in this regard. In terms of general safety pharmacology studies, SCH 34117 induced no effect on the rat gastrointestinal, renal or central nervous systems at oral doses up to 12 mg/kg.

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

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

Pharmacokinetics: SCH 34117 was generally well absorbed with an oral bioavailability of 45-94% observed in rats and 47-57% in monkeys. Plasma concentrations of SCH 34117 increased supra-proportionally with dose in rats and drug accumulation was evident. Systemic exposure was greater in females than in males. In monkeys, plasma SCH 34117 levels increased proportionally to surpa-portionally. Following loratadine administration, systemic exposure to SCH 34117 was greater in all species tested except for rabbits. Tmax was achieved within 4 hours in rabbits, mice and monkeys and 1.5-12 hours in rats; elimination half-life 2-5 hours in mice and rats and 8-11.3 hours in monkeys. Drug accumulation was evident and no gender differences were observed. In rats, SCH 34117 was widely distributed with highest levels detected in the pituitary, adrenal gland, lung, liver, spleen, thyroid, and mesenteric lymph nodes. Distribution of 14C-loratadine in pregnant rats demonstrated that radioactivity crossed the placental barrier equally at the post-embryonic period and near-term. Tissue distribution was similar in maternal and fetal tissues with lower levels found in the fetus. Plasma protein binding of SCH 34117 was variable across species as the mouse, rat, monkey and humans demonstrated 94.4%, 90.5%, 85.8% and 85.0% binding, respectively. The comparative species metabolism of SCH 34117 is summarized in Figure 1. SCH 34117 was extensively metabolized in rats, mice and monkeys and the metabolites are excreted either unchanged, as glucuronides or as further oxidized and conjugated products. Metabolism of SCH 34117 occurred through hydroxylation (primarily at the 5- and 6-positions and the 3-position to a lesser degree) and glucuronidation in the species tested. Hydroxylation at the 3-position was more extensive in humans. Male rats achieved relatively high circulating levels of SCH 357130 while N-oxidation was observed in monkeys. In vitro studies confirmed the results of the in vivo studies and demonstrated that the hydroxylated metabolites are formed in humans although unchanged SCH 34117 was the primary compound detected. The metabolism profile of SCH 34117 is generally similar to that of loratadine with no SCH 34117-specific metabolites formed. Excretion of SCH 34117-related radioactivity was primarily through the feces with a large portion contributed through the bile. Approximately 20-40% was excreted through the urine.

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



Acute Toxicity: Acute, oral and intraperitoneal studies in mice and rats, as well as an oral study in monkeys were submitted to IND[ ]. Maximum nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS and respiratory system in rats and mice and the gastrointestinal system in monkeys.

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

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

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

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

Chronic Toxicity: The similar toxicological findings following SCH 34117 and loratadine administration in the 3 month rat and monkey studies at similar exposure levels of SCH 34117 support bridging to the chronic loratadine toxicology program. Therefore, the Sponsor was not required to perform chronic toxicity studies with SCH 34117.

Reproduction: Effects of SCH 34117 on fertility were studies in both sexes. In females, oral doses up to 24 mg/kg (~ 560 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) did not influence fertility although preimplantation loss was increased and numbers of implantation sites and fetuses were decreased at this dose. In males, oral doses of 12 mg/kg (~ 180 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater reduced fertility (24-64%). A dose of 3 mg/kg (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no effect on fertility. General findings in males included reduced organ weights at the high-dose (prostate, testis, epididymis; 19-42%), small and soft testes at all doses, and microscopic findings at all doses (atrophy and degeneration of the seminiferous tubules, spermatid giant cells, spermatic cellular debris and oligospermia, reduced sperm numbers, production and motility at the mid- and high-doses). The number of implantation sites and viable embryos were reduced in females mated with mid- and high-dose males and the incidence of preimplantation loss was increased. The findings in males were generally non-reversible.

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

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

An oral peri- and post-natal study was performed in rats. A dose of 3 mg/kg SCH 34117 (~ 30 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) had no toxicologically significant effects on F_1 pup survival, pre-weaning growth or F_1 development. A dose of 9 mg/kg (~ 190 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose) or greater led to reduced fetal weight (8-12%) and a dose-related effect on righting reflex. No significant effects were observed in the F_2 generation at doses up to 24 mg/kg (~ 520 times the area under the plasma concentration versus time curve (AUC) for patients at the recommended daily oral dose).

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

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

Carcinogenicity: Carcinogenicity studies have not been performed with SCH 34117. A two-year study in rats and an eighteen-month study in mice performed with loratadine induced hepatic carcinogenicity in male mice and male and female rats. In addition, the mouse study was not considered to have achieved the maximum tolerated dose (MTD). The sponsor requested a waiver from performing carcinogenicity studies with SCH 34117 based upon SCH 34117 exposure ratios achieved during carcinogenicity studies performed with loratadine. CDER's Pharmacology/Toxicology Senior Policy Team considered the waiver request and concluded that the rat carcinogenicity study performed with loratadine sufficiently assesses the carcinogenic liability of SCH 34117 since the study resulted in an unbound DCL-derived rodent to human exposure multiple exceeding a factor of 25. However, the waiver for the mouse carcinogenicity study was not acceptable since appropriate SCH 34117 exposure multiples were not achieved in the carcinogenicity study with loratadine and the mouse study was not considered to have achieved an appropriate high dose. Thus, the sponsor was informed that a two-year mouse carcinogenicity study would be required. The Senior Policy Team felt that the study could be performed as a Phase 4 commitment since loratadine is an approved drug product and a significant portion of the population is already exposed to its metabolite SCH 34117, the genotoxicity studies for SCH 34117 resulted in negative findings and the carcinogenic potential has at least been partially assessed in the studies performed in rats and mice with loratadine. A study protocol was submitted by the sponsor for CAC concurrence and the Executive CAC

provided concurrence with changes in the proposed dose selection (see Exec CAC minutes dated August 3, 2000). The sponsor should submit the final study report within three years of the NDA approval or study initiation, whichever occurs first.

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

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

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

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

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

LABELING REVIEW:

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

DRAFT

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

DRAFT

RECOMMENDATIONS

1. 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.

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

/S/ 9/29/00

Timothy J. McGovern, Ph.D., Pharmacologist

/S/ Sept 29, 2000

Comment for letter to Sponsor:

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

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

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

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

Species	**DCL/14C ratio**	**Protein binding (%)**
Mouse	0.37	94.4
Rat	0.22	90.5
Human	0.08	85.6
Monkey	NA	85.8

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

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

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

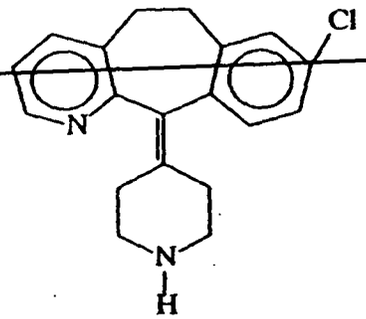
Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Schering-Plough Corporation

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

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

Structure:



Molecular Weight: 310.82

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

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

Class: Anti-histamine

Indication: Allergic rhinitis/chronic idiopathic urticaria

Clinical Formulation:

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

Route of Administration: Oral (tablet)

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

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

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

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

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

Preclinical Studies Submitted and Reviewed in this IND:

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

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

Studies Previously Reviewed: None

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

PHARMACOLOGY

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

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

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

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

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

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

---

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

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

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

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

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

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

[3] Cardelus, I, Puig, J, Bou, J, Jauregui, J, Fernandez, AG and Palacios, JM. (1997). Xerostomia and mydriasis: Two possible muscarinic peripheral side effects associated with descarboethoxyloratadine, the main metabolite of loratadine. Proc. British Pharmacological Soc.: P149.
[4] Ducic, I, Ko, CM, Shuba, Y, and Morad, M. (1998). Comparative effects of loratadine, and terfenadine on cardiac K^+ channels. J. Cardiovascular Pharmacol. In press.

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

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

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

In a second study cited by the sponsor, the effects of SCH 34117 on cardiac K^+ channel (hKv1.5) cloned from human ventricle and stably expressed in a mouse cell line (Ltk-) were assessed[5]. SCH 34117 blocked hKv1.5 channels, which generate the ultra-rapid delayed outward K^+ current in human atria, in a concentration-, voltage-, and time-dependent manner. SCH 34117 (1 to 100 μM) inhibited hKv1.5 current with an apparent affinity constant (K_D) of 12.5 μM, but was less potent than loratadine or terfenadine (K_D = 1.0 and 0.8 μM, respectively). Thus, the relative potency is terfenadine > loratadine > SCH 34117. The blockade by SCH 34117 increased over the voltage range, indicating that SCH 34117 binds preferentially to the open state of the channel. In addition, a concentration of 20 μM increased the time constant of deactivation of tail currents, thus inducing a "crossover" phenomenon.

Summary of Pharmacology

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

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

only at highest dose of 30 mg/kg po). SCH 34117 was also more potent than fexofenadine and carebastine, but less potent than atropine in inhibiting pilocarpine-induced acinar cell degranulation in the submandibular gland. SCH 34117 also produced a potent and long lasting (>120 min) mydriasis after topical administration (ED_{50} = 2.7 mg/kg), but did not affect oxotremorine hypothermia and OXO-induced tremor. Both SCH 34117 and loratadine were significantly less potent than terfenadine in inhibiting rat and guinea pig cardiac K^+ channels. SCH 34117 (1 to 100 μM) also inhibited a cloned human hKv1.5 current with an K_D of 12.5 μM, but was less potent than loratadine or terfenadine (K_D=1.0 and 0.8 μM, respectively).

SAFETY PHARMACOLOGY

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

PHARMACOKINETICS AND TOXICOKINETICS

Single/Multiple Dose Pharmacokinetics:

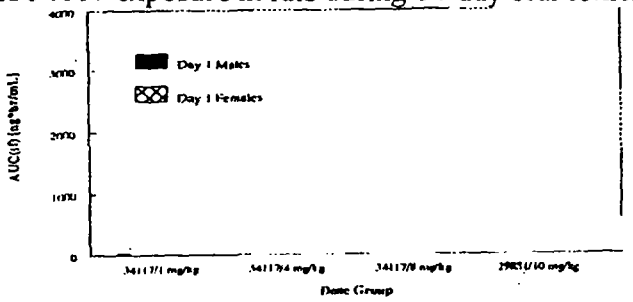
The toxicokinetics of two 14-day oral toxicity studies were submitted and are summarized briefly in Figures 1 (rat) and 2 (monkey), and in greater detail in the Toxicology section of this review. Exposures to SCH 34117 increased supra-proportionally with dose in the rat following oral administration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

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

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

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

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



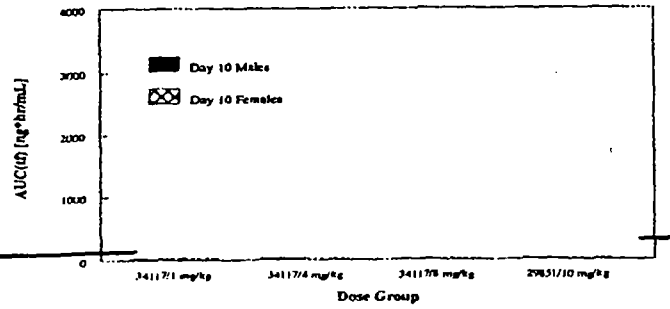
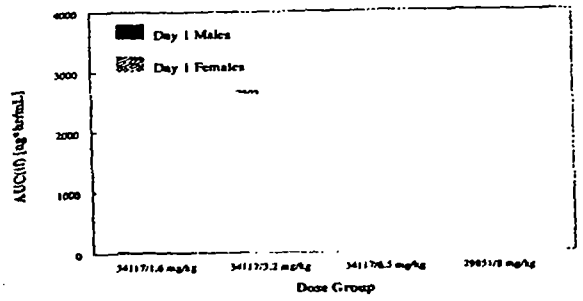


Figure 2. SCH 34117 exposure in monkeys during 14-day oral toxicity study.



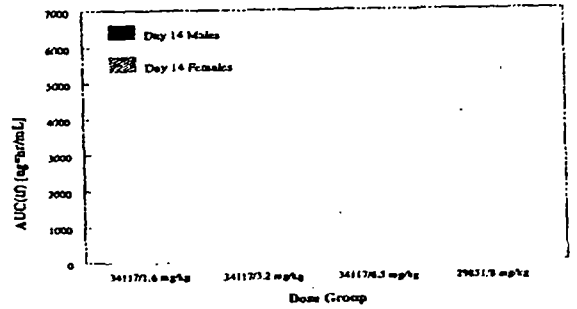


Table 4. Single dose toxicokinetics of SCH 34117 in humans.

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

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

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

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

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

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

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

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

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

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

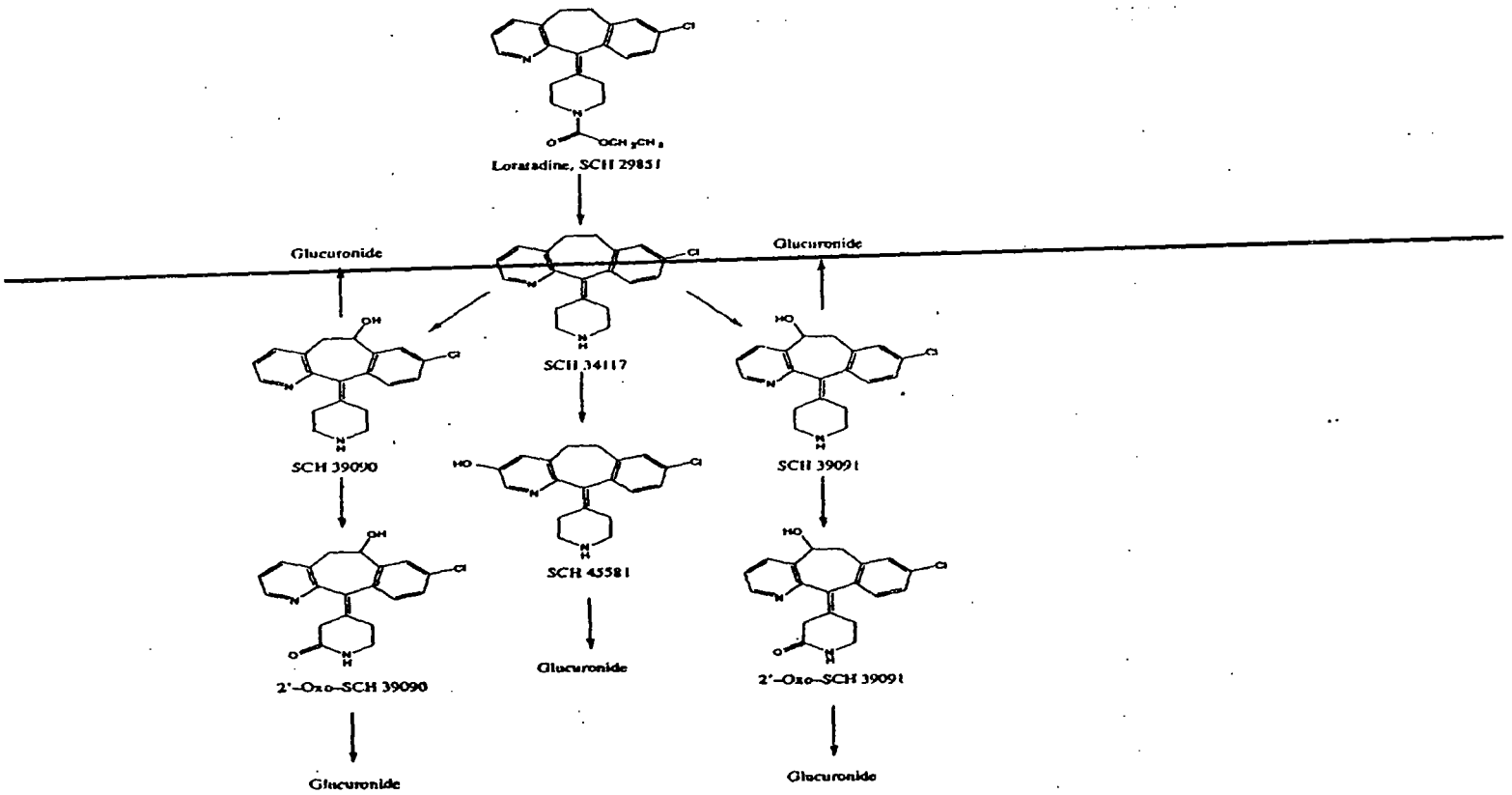


Table 6. Relative abundance of metabolites following oral, single dose administrations.

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

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

Summary of Pharmacokinetics and Toxicokinetics

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

Table 7. Comparative pharmacokinetics of SCH 34117.

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

TOXICOLOGY

ACUTE TOXICITY:

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

Mouse, Acute Oral Toxicity

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

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

Mouse, Acute Intraperitoneal Toxicity

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

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

Rat, Acute Oral Toxicity

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

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