34117 administration. However, metabolites specific to loratadine were detected in the pooled plasma and bile of male mice (monohydroxy loratadine glucuronide, monoketo-monohydroxy loratadine, monohydroxy loratadine glucuronide). In addition, previously unreported metabolites were observed in rat urine and plasma following dosing with SCH 34117 and loratadine (unknown metabolite RM1: m/z 323; 5,6-dihydroxy-SCH 34117, and three unknown metabolites RM3: m/z 339). Also, a significant portion of loratadine was hydroxylated directly without first being metabolized to SCH 34117 in the mouse.

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

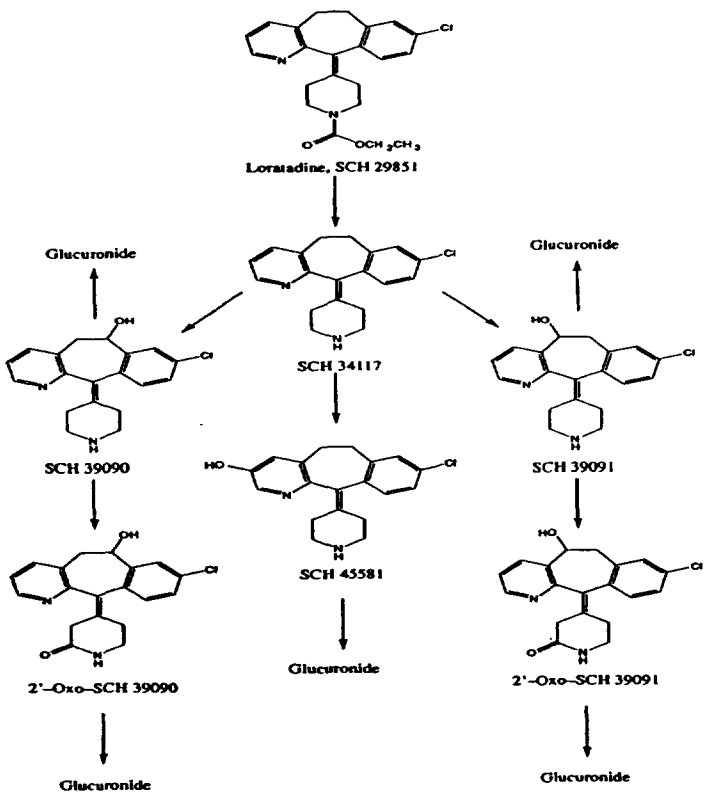

**Table 6.** Relative abundance of metabolites following oral, single dose administrations.

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

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

## Summary of Pharmacokinetics and Toxicokinetics

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

**Table 7.** Comparative pharmacokinetics of SCH 34117.

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

## TOXICOLOGY

*ACUTE TOXICITY:*

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

### Mouse, Acute Oral Toxicity

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

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

### Mouse, Acute Intraperitoneal Toxicity

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

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

### Rat, Acute Oral Toxicity

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

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

**Rat, Acute Intraperitoneal Toxicity**

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

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

**Monkey, Acute Rising Dose Oral Toxicity**

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

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

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

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

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

*MULTIPLE-DOSE TOXICITY:*

**Rat, 14-day Oral Toxicity**

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

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

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

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

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

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

**Results:** Results are summarized in tables 9-12.

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

*Clinical Observations:* No treatment-related effects.

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

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

*Ophthalmoscopy:* No toxicologically significant treatment-related effects.

*Hematology:* No toxicologically significant treatment-related effects.

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

**Table 9.** Clinical observations and chemistry findings in rats.

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

*Urinalysis:* No toxicologically significant treatment-related effects.

*Organ Weights:* No toxicologically significant treatment-related effects.

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

**Table 10.** Enzyme induction in rats.

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

**Shaded areas indicate a significant difference from vehicle controls.**

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

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

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

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

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

*Toxicokinetics:* Table 12 summarizes the results of the toxicokinetic analysis in which plasma levels were measured using [redacted] Exposures to SCH 34117 increased supra-proportionally with dose following oral administration on Day 1 as 4- and 8-fold increases in dose resulted in 5.4- to 9.9-fold and 22.8- to 34.7-fold increases, respectively, in exposure. Exposures were generally greater at Day 10 compared to Day 1 at doses > 1 mg/kg/d, indicating the potential for drug accumulation, and 4- and 8-fold increases in dose resulted in 23- to 35-fold and 50- to 61-fold increases, respectively, in exposure. In addition, exposure levels in females

were consistently greater (1.6- to 4.9-fold) than in males. Maximum plasma concentrations also increased supra-proportionally compared to dose, but not to the extent of AUC. Mean $T_{max}$ was achieved between 2.5-12 hours on Day 1, increasing with increasing dose, and at 2.5 hours on Day 10. The terminal phase half-life was approximately 2-4 hours following administration.

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

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

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

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

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

**Rat, 14-day Oral Toxicity**

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

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

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

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

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

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

**Results:** Results are summarized in tables 13-16.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| Dose (mg/kg/d) | Day | 3-hr plasma concentration (ng/ml) | | Day | 24-hr urinary recovery (%) | |
|---|---|---|---|---|---|---|
| | | Males | Females | | Males | Females |
| 15 | 1 | 284 | 264 | 1 | 2.35 | 4.80 |
| | 13 | 257 | 357 | 12 | 2.45 | 3.43 |
| 60 | 1 | 417 | 646 | 1 | 2.90 | 3.63 |
| | 13 | 1046 | 1207 | 12 | 2.23 | 7.1 |
| 240 | 1 | 572 | 911 | 1 | 1.15 | 1.45 |
| | 13 | * | * | 12 | * | * |

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

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

**Monkey, 14-day Oral Toxicity**

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

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

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

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

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

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

**Results:** Results are summarized in tables 17-20.

*Mortality:* None.

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

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

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

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

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

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

*Hematology:* No toxicologically significant treatment-related effects.

*Clinical Chemistry:* No toxicologically significant treatment-related effects were observed other than a dose-dependent increase in triglyceride levels (25-126%) in SCH 34117-treated males (Table 17). Levels in high-dose males were increased by 62% prior to dosing, indicating a net increase of 64% after dosing. In addition, males administered loratadine showed a 44% increase in triglyceride levels compared to controls. However, prior to dosing, levels were increased by 56%, resulting in a net decrease of 12%.

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

**Table 17.** Clinical findings in monkeys administered SCH 34117.

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

*Organ Weights:* No toxicologically significant treatment-related effects.

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

**Table 18.** Enzyme induction in monkeys administered SCH 34117.

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Dose (mg/kg/d)* | 0 | 1.6 | 3.2 | 6.5 | Lorat. | 0 | 1.6 | 3.2 | 6.5 | Lorat. |
| **Microsomal prot.** (mg/g liver) | 22.6 | 20.8 | 22.5 | 21.2 | 24.0 | 21.8 | 21.4 | 22.6 | 24.7 | 24.1 |
| **Enzyme Induction** | | | | | | | | | | |
| PROD (pmol/min/mg mic. prot.) | 1.1 | 0.9 | 1.3 | [redacted] | | 2.5 | 3.2 | 3.4 | [redacted] | |
| EROD (pmol/min/mg mic. prot.) | 469 | 569 | 540 | [redacted] | | 304 | 433 | 602 | [redacted] | |

**Shaded areas indicate a significant difference from vehicle controls.**

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

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

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

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

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

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

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

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

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

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

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

## Summary of Toxicology

Acute, oral and intraperitoneal studies were performed in mice and rats, as well as an oral study in monkeys. Maximum nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS (hypoactivity, ataxia, convulsions, tremors, prostration) and respiratory system (gasping, increased respiratory rate) in mice and rats, and the gastrointestinal system (emesis, diarrhea) in monkeys.

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

**Addendum: Histopathology inventory for IND .**

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

* Organ weight obtained

## REPRODUCTIVE TOXICOLOGY

### Rat (oral) Pilot Segment I Reproductive Toxicity Study

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

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

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

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

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

**Results:** Results are summarized in Table 21.

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

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

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

*Necropsy*: No abnormal findings were observed.

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

*Vaginal cytology*: No abnormalities were observed.

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

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

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

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

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

**Rat (oral) Pilot Segment II Reproductive Toxicity Study**
*Report No.*: P-6718 *Study No.*: 97113 *Volume*: 1.16

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

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

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

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

**Results:** Results are summarized in Table 22.

*Mortality*: None.

*Clinical signs*: None

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

*Necropsy*: No abnormal findings were observed.

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

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

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

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

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

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

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

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

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

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

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

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

**Results:**

**Phase I:** Deaths occurred at doses ≥ 150 mg/kg/day (7 doses at 150 mg/kg, 3 doses at 225 mg/kg and 2 doses at 300 mg/kg). At 150 and 225 mg/kg, reduced stool was observed prior to death. Animals given 100 or 50 mg/kg were dosed for 5 or 3 days, respectively, and observed for 7 days. No unusual clinical signs or necropsy findings were observed. Food consumption was reduced in rabbits dosed with ≥ 100 mg/kg (graded as "ate poorly") and body weights were suppressed in all rabbits during the dosing period (3-13%). Food consumption in the rabbit given 100 mg/kg returned to normal within a day after dosing was stopped.

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

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

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

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

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

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

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

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

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

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

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

*Study Dates:* Starting date 9/12/97; report issued 2/10/98
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ
*Test Article:* SCH 34117 (Batch 97-11001-139 and 97-34117-X-02RA; purity = NA) in 0.4% (w/v) aqueous methylcellulose
*Concentration:* 7.5-30 mg SCH 34117/ml
*Dose Volume:* 2 ml/kg/day
*GLP:* The study was an unaudited report.
*QA report:* No.

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

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

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

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

**Results:**

*Mortality:* None.

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

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

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

*Necropsy:* No treatment-related effects.

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

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

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

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

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

**Summary of Reproductive Toxicology Studies**

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

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

## GENETIC TOXICOLOGY

### In vitro Reverse Mutation Assay (Ames Assay)

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

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

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

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

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

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

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

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

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

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

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

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

**Chromosome Aberration Study in Human Peripheral Lymphocytes**
*Report No.*: P-6692 Study No.: *Volume:* 1.16

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

**Methods:** A series of chromosome aberration assays were performed ± metabolic activation (S9 fraction from Aroclor 1254-treated rats) using whole blood from two healthy donors, one male and one female. Duplicate cultures were exposed to either negative controls, solvent control, doses of SCH 34117 (adjusted in duplicate assays for toxicity) or doses of positive control. Assays were conducted with 24 and 48 hour treatment times without metabolic activation (male: 6.25-1500 µg/ml; female: 6.25-125 µg/ml) followed by 27 and 51 hour harvests, respectively. In addition, assays with a 3 hour treatment time ± metabolic activation (male: 6.25-1500 µg/ml; female: 12.5-200 µg/ml) followed by ~ 24 and 48 hour harvests were performed. The test drug was dissolved in 50% ethanol, while the positive controls, mitomycin C (for the nonactivation assays) and cyclophosphamide (for the activation assays) were dissolved in sterile deionized water. The mitotic index was assessed by analyzing the number of mitotic cells in 1000 cells/ culture. Cultures with a mitotic index < 40% of the solvent control were not scored for chromosome aberrations. One hundred cells, if possible, were analyzed from each duplicate culture for chromosome aberrations at the four highest dose levels of SCH 34117 (3 in the assay with metabolic activation, ~ 3 hr treatment and 24 hr harvest, donor 1), the negative control, solvent control and at one dose level of the positive control. At least 25 cells were analyzed from those cultures with greater than 25% of cells with one or more aberrations. In addition, the percentages of polyploidy and endoreduplication from at least one hundred cells from each duplicate culture were analyzed. A response was considered positive if the test article induced statistically significant increases in the number of cells with aberrations over those of the solvent controls at one or more concentrations in two donors and the increases showed a positive dose-

response, or if the test article induced statistically significant increases in the number of cells with chromosome aberrations in at least two consecutive concentrations in two donors.

**Results:** Osmolality of the test sample was comparable to that of the solvent control. The pH of the test sample was 8.5 versus 8.0 for the solvent control. In all assays a precipitate was formed at doses of 500 to 1500 µg/ml. Lysis was also observed after dosing with 1000 and 1500 µg/ml; and at the time of washing the cell cultures at 125-1500 µg/ml.

Under the conditions tested in this assay, SCH 34117 did not induce chromosomal aberrations, polyploidy or endoreduplication in cell cultures with or without metabolic activation at doses up to 15 µg/ml and 10 µg/ml (male and female donor, respectively: 24 hour treatment/27 hour harvest without metabolic activation), 25 and 10 µg/ml (male and female donor, respectively: 48 hour treatment/51 hour harvest without metabolic activation), 125 and 100 µg/ml (male and female donor, respectively: 3 hour treatment/24 hour harvest with metabolic activation), 125 and 130 µg/ml (male and female donor, respectively: 3 hour treatment/48 hour harvest with metabolic activation) and 90 and 50 µg/ml (male and female donor, respectively: 3 hour treatment/24 hour harvest without metabolic activation). Doses above those cited above induced levels of cytotoxicity which lead to mitotic indices < 40% and these cultures were not assessed for chromosomal aberrations. Increased incidences of chromosome aberrations were observed in cultures dose with the positive control agents, cyclophosphamide and mitomycin C. Negative and solvent controls were within historical ranges.

SCH 34117 is considered negative for inducing chromosome aberrations in cultured whole blood human lymphocytes from a male and female donor in the presence or absence of an exogenous metabolic activation system at doses up to 125 µg/ml in the male donor and 130 µg/ml in the female donor.

## OVERALL SUMMARY AND EVALUATION

**Pharmacology:** SCH 34117 displayed a 14-fold greater affinity for the $H_1$-receptor than loratadine and was more up to 20-fold more potent than loratadine in its antihistaminic activity in guinea pigs. The potency of the two compounds was comparable in inhibiting histamine-induced airway effects in monkeys. SCH 34117 also showed a similar affinity for $M_1$ and $M_3$-receptors, but not for $M_2$-recptors. In comparison, loratadine displayed no affinity for muscarinic receptors. SCH 34117 dose-dependently expressed anticholinergic activity by decreasing the spontaneous right atrial rate in male [redacted] 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%) only at highest dose of 30 mg/kg po). SCH 34117 was more potent than fexofenadine and carebastine, but less potent than atropine in inhibiting pilocarpine-induced acinar cell degranulation in the submandibular gland. SCH 34117 also produced a potent and long lasting (>120 min) mydriasis after topical administration ($ED_{50}$ = 2.7 mg/kg), but did not affect oxotremorine hypothermia and

OXO-induced tremor. Both SCH 34117 and loratadine displayed limited potency in inhibiting rat and guinea pig cardiac $K^+$ channels. SCH 34117 (1 to 100 μM) also inhibited a cloned human hKv1.5 current with an $K_D$ of 12.5 μM, but was less potent than loratadine or terfenadine ($K_D$ = 1.0 and 0.8 μM, respectively).

**Safety Pharmacology:** In a study cited by the sponsor and included in the IND package, loratadine (30 and 100 mg/kg, iv) did not alter cardiovascular parameters in the guinea pig (plasma levels = 27.8-61 μg/ml). Resulting SCH 34117 concentrations (1.46 μg/ml) were 370X greater than its $C_{max}$ in man after a single oral dose of 10 mg loratadine. However, terfenadine, quinidine and diphenhydramine induced significant cardiovascular and ECG effects. This study, in combination with in vitro assessments of rat and guinea pig cardiac K+ channels and the 14-day oral toxicity study in monkeys, suggests that SCH 34117 does not possess significant cardiovascular activity. The acting Medical Officer, Dr. Peter Honig, was consulted and agreed that no further preclinical assessment of cardiovascular effects is necessary.

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

**Acute Toxicity:** Acute, oral and intraperitoneal studies were performed in mice and rats, as well as an oral study in monkeys. Maximum nonlethal doses, oral and intraperitoneal, of 250 and 25 mg/kg, respectively, and minimum lethal doses of 500 and 50 mg/kg, respectively, were observed in mice. In the rat, maximum nonlethal doses, oral and intraperitoneal, were 125 and 25 mg/kg, respectively, and the minimal lethal doses were 250 and 50 mg/kg, respectively. No

mortalities were observed in the acute monkey study at doses up to 250 mg/kg. Targets of acute toxicity appeared to be the CNS and respiratory system in rats and mice and the gastrointestinal system in monkeys.

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

**Reproductive Toxicology:** In a Segment I study in rats (6-48 mg/kg SCH 34117, oral) most treatment-related effects were observed at the high-dose and included one death (female), reduced stool, large fecal pellets, reduced premating body weight gain and male and female mating indices, although no clear effects on fertility were observed. Time to identify positive evidence of mating was also increased (143 to 325%) at the mid- and high-dose. Reproductive effects included reduced corpora lutea/animal, fewer implantation sites and fetuses and an increased number of early resorptions/animal at the high-dose. A NOAEL of 24 mg/kg and a lethal dose of 48 mg/kg were identified for this study. The sponsor should consult ICH guidelines for reproductive toxicology studies when initiating the definitive Segment I study, as males were dosed for only 21 days prior to mating in this pilot study. In a pilot Segment II study (3-48 mg/kg), significant findings in female rats included reduced maternal body weight gain during the dosing period (upper-middle and high-dose animals) and fetal body weights at the high-dose. A NOAEL of 12 mg/kg was identified in this study. The high-dose in the definitive rat Segment I and Segment II studies should be less than 48 mg/kg and should not exceed 48 mg/kg, respectively.

In the pilot Segment II study in rabbits (25 to 100 mg/kg), clinical signs included deaths, lack of stool, soft stool, small fecal pellets, reduced number of fecal pellets and reduced body weight and food consumption. Effects on reproduction parameters, unavailable for the high-dose group due to maternal mortality, were not evident in the low- and mid-dose groups and no findings were observed during the fetal examination. A NOAEL of 50 mg/kg was identified in this study and the high-dose in a definitive embryo-fetal development study should be between 50 and 100 mg/kg/day. Preliminary findings from the definitive Segment II study (15-60 mg/kg) included a

change in formed stool at the mid- and high-dose and in some low-dose rabbits, as well as reduced mean body weight gain at the high-dose. Although an increased number of resorptions occurred in the high-dose group, no changes in fetal body weight or gross/skeletal examinations were observed. Exposure increased dose-proportionally between 15 and 30 mg/kg and supra-proportionally between 30 and 60 mg/kg and plasma concentrations peaked within 3 hours. A preliminary NOAEL of 30 mg/kg was identified and the sponsor should submit a complete report of this study.

**Genotoxicity:** SCH 34117 was negative in the bacterial mutation test (Ames assay) using the plate incorporation method at concentrations up to 1500 µg/plate. SCH 34117 was also negative in a chromosome aberration assay in cultured whole blood human lymphocytes in the presence or absence of an exogenous metabolic activation system at doses up to 125 µg/ml in the male donor and 130 µg/ml in the female donor. Significant cytotoxicity occurred at doses higher than the maximum reported.

The sponsor has proposed a Phase II, multiple-dose study to examine the clinical efficacy and safety of SCH 34117 (2.5-20 mg/day) for 2 weeks in patients with seasonal allergic rhinitis. The preclinical 14-day studies in rats and monkeys resulted in NOAELs of 8 and 6.5 mg/kg/day, respectively, although both studies resulted in numerous histological findings of slightly greater incidence at the high dose compared to control groups. A definitive assessment of these findings could not be determined since the sponsor did not evaluate the tissues of the low- and intermediate-dose groups. However, these findings are not of great concern since they were of generally low severity and did not fit within the general toxicity profile of SCH 34117 and its parent compound loratadine. Furthermore, the expected exposure levels in clinical trials at the proposed maximum dose of 20 mg/day should be considerably less than those reported in the preclinical studies. A previously completed Phase I single-dose study (2.5-20 mg) in healthy male volunteers resulted in a mean AUC of 158 ng.h/ml at the high-dose. This exposure level could reasonably be expected to rise to 300 ng.h/ml in a 14-day study, assuming drug accumulation observed in clinical trials with loratadine. An exposure of this level is still considerably below those observed in rats and monkeys at the doses in which the questionable histological findings were observed. Thus, the proposed clinical trial is considered to be reasonably safe to proceed.

## RECOMMENDATIONS

1. The clinical trial may proceed as proposed (up to 20 mg SCH 34117/day for 14 days).

2. In the future, the sponsor should evaluate tissue histopathology from low- and intermediate-dose groups when high-dose groups show a higher incidence than control groups.

3. The sponsor should complete a full histological examination of all tissues and organs in future toxicity studies.

4. The submitted pilot Segment I reproduction toxicity study in rats consisted of a 3-week premating administration interval in males. It should be noted that ICH Guidelines for Detection of Toxicity to Reproduction (ICH S5A and S5B) recommend premating administration for males to be 4-weeks in duration, assuming that a toxicity study of at least 1-month duration demonstrates no effects on spermatogenesis (premating administration of 9-10 weeks in the case of positive findings). The sponsor should consult the ICH Guidelines when performing the definitive Segment I and other reproductive toxicology studies.

5. The sponsor should submit a complete report of the Segment II reproduction toxicology study in rabbits (Study No. P-6802) when it becomes available.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

**Draft Comments for Letter to Sponsor:**

1. In the future, tissue histopathology from low- and intermediate-dose groups should be evaluated when high-dose groups show an increased incidence or severity compared to control groups.

2. A full histological survey of tissues/organs should be performed in future toxicity studies.

3. The ICH Guidelines for Reproduction Toxicology (S5A and S5B) should be consulted when performing the definitive Segment I and other reproductive toxicology studies.

4. Please submit a complete report of the Segment II reproduction toxicology study in rabbits (Study No. P-6802) when it becomes available.

Original IND
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/P. Honig
HFD-570/G. Trout
HFD-570/T.J. McGovern

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

**IND No.** [redacted] **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):**

| Review Type | Date of Submission(s) | Reviewer | Date of Review |
|---|---|---|---|
| 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:**

| Study | Report # | Volume |
|---|---|---|
| ***Sub-chronic Toxicology:*** | | |
| Three-month dose-range finding study of SCH 34117 in mice | SN 97253 | 44.6 |
| ***Genetic Toxicology:*** | | |
| 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 ( [redacted] submitted to NDA 21-165) was submitted to IND [redacted] 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 [redacted] or [redacted] 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 (Crl/CD-1 BR VAF/Plus; 6 weeks old, 18.9-31 g) were assigned to the following treatment groups:

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

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

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

Organ weights . . . . . at sacrifice (organs included brain, epididymides, heart, kidneys, liver, lungs, ovaries, salivary glands, spleen, testes, thymus, uterus)
Sperm analysis . . . . . assessed in control and mid-high dose males
Gross pathology . . . . . at sacrifice
Histopathology . . . . . at sacrifice, all tissues were examined in the control (vehicle) and high-dose mice (for specific tissues/organs see Addendum, page 18). Target organs were evaluated to the no-effect level and all tissues from mice that died.

ıetics . . . . . 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 | Females | | | | | Males | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (mg/kg)** | 0 | 24 | 48 | 96 | 192 | 0 | 24 | 48 | 96 | 192 |
| Feces - enlarged | 0 | 0 | 10 | 10 | 10 | 0 | 0 | 10 | 10 | 10 |
| Hunched posture | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 1 |
| Dehydration | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| Hypoactivity | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 |

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

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

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

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

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

*Ophthalmoscopy:* No treatment-related findings were reported.

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

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

| | 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.

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

**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 | [illegible] | [illegible] | | ↑6 | ↑9 | [illegible] | [illegible] |
| Liver/Body wt ratio | | | | | | | | | | |
| % Δ from control | | ↑4 | ↑12 | [illegible] | [illegible] | | ↑6 | ↑8 | [illegible] | [illegible] |
| Microsomal protein (mg/tot liver) | | | | | | | | | | |
| % Δ from control | | ↑4 | ↑11 | [illegible] | [illegible] | | ↑19 | ↑34 | [illegible] | [illegible] |
| Cytochrome P450 | | | | | | | | | | |
| % Δ from control | | no Δ | no Δ | no Δ | ↓30 | | [illegible] | [illegible] | [illegible] | [illegible] |
| Nmol/mg microsomal protein | | ↓5 | ↑3 | ↑35 | ↓12 | | ↑45 | [illegible] | [illegible] | [illegible] |
| Nmol/g liver | | ↑4 | ↑10 | ↑59 | ↑19 | | ↑53 | [illegible] | [illegible] | [illegible] |
| Nmol/total liver | | | | | | | | | | |
| **Enzyme Induction** | | | | | | | | | | |
| % Δ from control | | | | | | | | | | |
| PROD | | | | | | | | | | |
| pmol/min/mg micros. protein | | [illegible] | [illegible] | [illegible] | ↓11 | | [illegible] | ↑280 | [illegible] | ↓33 |
| pmol/min/g liver | | [illegible] | [illegible] | [illegible] | ↑13 | | [illegible] | [illegible] | [illegible] | ↑7 |
| pmol/min/total liver | | [illegible] | [illegible] | [illegible] | ↑49 | | [illegible] | [illegible] | [illegible] | ↑43 |
| EROD | | | | | | | | | | |
| pmol/min/mg micros. protein | | ↑180 | ↑150 | ↑312 | [illegible] | | [illegible] | [illegible] | ↑160 | ↑233 |
| pmol/min/g liver | | ↑160 | ↑151 | ↑439 | [illegible] | | ↑81 | ↑134 | [illegible] | [illegible] |
| pmol/min/total liver | | ↑181 | ↑173 | ↑542 | [illegible] | | ↑90 | ↑154 | [illegible] | [illegible] |

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 CYP2B1/2may 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 | | | |
|---|---|---|---|---|---|---|---|---|
| Dose group (mg/kg) | 24 | 48 | 96 | 192 | 24 | 48 | 96 | 192 |
| Liver | | | | | | | | |
| AOW-% Δ from control | 5 | 6 | 15 | 29 | 7 | 13 | 36 | 40 |
| RTB-% Δ from control | 5 | 12 | 26 | 71 | 6 | 11 | 34 | 69 |
| Lungs | | | | | | | | |
| AOW-% Δ from control | 5 | -5 | 5 | 10 | no Δ | 6 | 11 | 11 |
| RTB-% Δ from control | 5 | no Δ | 14 | 46 | 1 | 1 | 8 | 36 |
| Thymus | | | | | | | | |
| AOW-% Δ from control | -7 | -7 | -17 | -41 | -29 | 3 | -19 | -47 |
| RTB-% Δ from control | -7 | -2 | -10 | -22 | -30 | 1 | -21 | -36 |
| Uterus | | | | | | | | |
| AOW-% Δ from control | | | | | -14 | -18 | -33 | -48 |
| RTB-% Δ from control | | | | | -14 | -20 | -38 | -39 |

AOW: Absolute organ weight RTB: Relative to body weight

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

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

| Observation | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | 0 | 24 | 48 | 96 | 192 | 0 | 24 | 48 | 96 | 192 |
| 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.