CENTER FOR DRUG EVALUATION AND RESEARCH

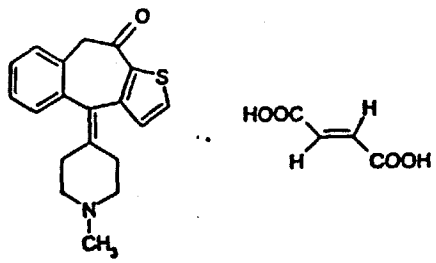
APPLICATION NUMBER: **21-066**

PHARMACOLOGY REVIEW(S)

THE DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMIC DRUG PRODUCTS

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA N^{o}:	21-066
SUBMISSION DATE:	December 31, 1998
REVIEWER RECEIPT DATE:	January 11, 1999
INFORMATION TO SPONSOR:	Yes (X), No ( )
REVIEWER:	Zhou Chen, Ph.D. (HFD-550)
DRAFT REVIEW COMPLETED:	May 17, 1999
DRUG NAME:	Ketotifen fumarate ophthalmic solution (0.025% ketotifen base), DR 42013
SPONSOR:	CIBA Vision 11460 Johns Creek Parkway Duluth, Georgia 30097
RELATED SUBMISSIONS:	
DRUG CLASS:	
INDICATION:	For the prevention of itching of the eye due to allergic conjunctivitis
PROPOSED DOSE:	50 µl in the affected eye every 8 to 12 hr (Total dose could be 0.075 mg/patient/day or 0.0015 mg/kg, 0.0555 mg/m^2 for a 50 kg adult)
ROUTE OF ADMINISTRATION:	Ocular, topical
FORMULA:	$C_{19}H_{19}NOS$, MW: 309.43 4-(1-methyl-4-piperidylidene)-4H-benzo [4,5] cycloheptа [1,2-b] thiophen-10 (9H)-one hydrogen fumarate



FORMULATION:

Component	Standard quantity per ml (mg)
Ketotifen fumarate	0.345 (equivalent to 0.25 mg ketotifen)
Glycerin USP	
Benzalkonium chloride NF	
Sodium hydroxide, NF	
Hydrochloride acid, NF	
Water, purified, USP (distilled)	

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NDA 21-066 Ketotifen Fumarate Ophthalmic Solution 0.025%

BACKGROUND:

Ketotifen is a selective, non-competitive antagonist of histamine (H_1-receptor). Pharmacologic studies indicated that ketotifen can inhibit anaphylaxis allergic reactions through several mechanisms. Oral ketotifen has been approved in Japan, Canada and European countries for the treatment of asthma. Ophthalmic ketotifen fumarate 0.05% was investigated in Japan and was judged as effective, safe and well tolerated. The drug has been marketed in Japan since 1991. The sponsor, CIBA Vision, is developing ketotifen fumarate ophthalmic solution 0.025% in the United States for the temporary prevention of itching of the eye due to allergic conjunctivitis.

PREVIOUS HUMAN EXPERIENCE:

Ketotifen fumarate ophthalmic solution has been studied in humans in several clinical trials and has been on the market in Japan since 1991. The drug was described as efficacious, safe and well tolerated. No serious side effects have been reported. The adverse effects observed included burning and itching, discharge, dry eye, conjunctival injection, headache and rhinitis.

NONCLINICAL STUDIES:

Reviewer's Comments: Several studies were conducted under

Pharmacology:

Studies reviewed:

Mechanism of action and activity related to proposed indication

1. Antianaphylactic effects. Vol. 7, Page 160.
2. Antihistaminic activity. Vol. 7, Page 168.
3. Antiserotonin activity. Vol. 7, Page 178.
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7. Dissociation of antianaphylactic and antihistaminic activities. Vol. 7, Page 216.
8. Inhibition of chemical mediator release from human leukocytes by HC 20-511 (ketotifen). Vol. 7, Page 228.
9. Effects of cyproheptadine, ketotifen and sodium nitroprosside on mechanical activity and calcium uptake in guinea pig taenia coli in vitro. Vol. 7, Page 265.
10. β-adrenergic tachyphylaxis in the rat and its reversal and prevention by ketotifen. Vol. 7, Page 278.
11. Comparative pharmacological investigations with the (+) and (-) antipodes of HC 20-511 (34-145 and 34-146 respectively). Vol. 7, Page 338.

12. Comparative pharmacological investigations with two metabolites of ketotifen, the N-oxide (21-829) and nor-ketotifen (21-830). Vol. 7, Page 349.
13. Effects of ketotifen fumarate eye drops on experiential conjunctivitis in rats and guinea pigs. Vol. 8, Page 001.
14. Effects of [redacted]almide, naaxia, opticron, [redacted]DR 15015 and DR 15016 on ocular immediate hypersensitivity in the albino rat (compound 48/80 model). Vol. 8, Page 012.
15. Ketotifen and olopatadine. Effect on ocular immediate hypersensitivity in the albino rat (compound 48/80 model). Vol. 8, Page 055.
16. Effect of [redacted]almide, naaxia, opticron, [redacted]DR 15015 and DR 15016 on ocular active anaphylaxis in the guinea pig (compound 48/80 model). Vol. 8, Page 093.
17. Ketotifen and olopatadine. Effect on ocular active anaphylaxis in the guinea pig (compound 48/80 model). Vol. 8, Page 134.
18. Effect of ketotifen and olopatadine on eosinophil infiltration into the guinea pig conjunctiva. NDA supplement submitted 4-30-99, Page 169.

Safety pharmacology

19. Cardiovascular activities. Vol. 7, Page 183.
20. Renal actions. Vol. 7, Page 194.
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22. Local anaesthesia in the rat. Vol. 7, Page 202.
23. The effects of ketotifen (HC 20-511 hfu) in the gross behavior in Cebus monkeys. Vol. 7, Page 304.
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25. Actions in immunopharmacological models. Vol. 7, Page 329.

Review:

Mechanism of action and activity related to proposed indication

1. Antianaphylactic effects. Vol. 7, Page 160.

A. Passive cutaneous anaphylaxis (PCA) in the rat

Female rats were passively sensitizened by intradermal injection with antiserum at 3 sites on the back. Twenty-four hr later they were treated with ketotifen by iv or oral administration followed by intradermal injection of histamine or [redacted]at 2 other sites. A cutaneous anaphylactic reaction was then elicited by iv injection of ovalbumin in 0.9% saline containing 0.25% Evans blue dye. The intensity was determined by measuring the diameter of blue spot at each antiserum, histamine and serotonin injection site. ED_{50} was determined as the drug dose decreasing the diameter of the blue area by 50%. The results indicated that HC 20-511 inhibited both antibody-antigen-induced **anaphylactic** effect (ED_{50} = 0.299 mg/kg iv and 5.1 mg/kg po) and histamine-induced **anaphylactoid** reaction (ED_{50} = 0.228 mg/kg iv and 0.232 mg/kg po). No effects on [redacted]induced

responses were observed. In the same study, disodium cromoglycate (DSCG, histamine release inhibitor) showed inhibitory effects only on anaphylactic responses after iv administration (ED_{50} = 2.74 mg/kg). [redacted] an H_1-receptor antagonist, showed only antihistamine effects (ED_{50} = 0.233 mg/kg, iv).

B. Antigen-induced increase in airways resistance in the anaesthetized, sensitized rat
C. 48/80-induced histamine release from rat isolated peritoneal mast cells
D. Substance effect on rat isolated peritoneal mast cells
E. Passive peritoneal anaphylaxis in the rat

These studies were reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Pages 49-51.

2. Antihistaminic activity. Vol. 7, Page 168.

A. Histamine-induced bronchospasm in the artificially-ventilated, anaesthetized guinea-pig

Anaesthetized guinea pigs were administered 50 µg/kg of histamine dihydrochloride by iv injection to induce bronchospasms. HC 20-511 (0.01-0.1 mg/kg) and [redacted] (0.05-0.3 mg/kg) were given 5 and 20 min before the induction of bronchospasms. The ED_{50} calculated in this study represented the dose level that produced 50% inhibition of the histamine-induced bronchospasms. The results indicated that the antihistaminic activity of HC 20-511 was 2 to 4 times greater than that of [redacted] (ED_{50}: HC 20-511 at 5 and 20 min 0.037 and 0.014 mg/kg, respectively; [redacted] at 5 and 20 min 0.103 and 0.056 mg/kg respectively). In the same study, DSCG at up to 5.6 mg/kg produced no inhibitory effects.

B. Histamine-induced bronchoconstriction in the conscious guinea-pig
C. Histamine-induced lethality in the conscious guinea-pig

These studies were reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 46.

D. Histamine-induced hypotension in the anaesthetized cat

The hypotensive response was elicited by iv injection of 2 µg/kg histamine dihydrochloride in anesthetized cats. As soon as the depressor response was constant, the test substances were administered. Two, 20 or 50 min later the next histamine dose was given. The ED_{50} calculated in this study represented the dose levels that inhibited the histamine-induced fall in blood pressure by 50%. The results are presented in the table below.

Inhibition of histamine-induced hypotension in cats

	HC 20-511			[redacted]	
Pretreatment interval (min)	5	20	50	5	20
ED50 (mg/kg, iv)	0.0067	0.0065	0.0062	0.061	0.059

E. Serum shock in the conscious, sensitized guinea-pig

This study was reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 48.

F. Histamine-induced contraction of the isolated guinea-pig

The accumulated doses of histamine induced contractions in isolated guinea-pig ileum. The dose-response curve was inhibited by HC 20-511 with a pD_2 value of 8.55.

G. Histamine-induced whealing response in the monkey skin

This study was reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 48.

3. Antiserotonin activity. Vol. 7, Page 178.

A. [redacted] induced lethality in the conscious guinea-pig

Guinea pigs were administered (sc or po) with HC 20-511 3 hr before being injected iv with a fatal dose of [redacted] (110 mg/kg). The ED_{50} calculated in this study represented the dose of drug that protected 50% of the animals against death due to [redacted] The results showed that HC 20-511 inhibited the lethal effects of [redacted] (ED_{50}: 3.5-5.9 mg/kg for SC and 9 mg/kg for po). Based on the ED_{50} of 0.004 mg/kg in the study "Histamine-induced lethality in the conscious guinea-pig", HC 20-511 was 1000 times more active against histamine than against [redacted]

B. [redacted] induced contractions of the isolated rat uterine horns

The contractions of isolated rat uterine horns were inhibited by HC 20-511 with a pA_2 value of 7.16, which indicated that HC 20-511's [redacted] effects were not great.

4. Acetylcholine-induced lethality in the conscious guinea-pig. Vol. 7, Page 181.

This study was reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 53.

5. Phosphodiesterase inhibition. Vol. 7, Page 181.

HC 20-511's effects on phosphodisterase activity in rat mast cells and heart and lung tissues were measured. The IC_{50} values were 6.3×10^{-4}M, 2.5×10^{-4}M and 2.5×10^{-4}M, in mast cells, heart and lung tissues, respectively.

6. Effect of HC 20-511 on 48/80-associated Ca^{++} uptake in mast cells. Vol. 7, Page 206.

The purpose of this study was to determine whether HC 20-511 inhibited 48/80-related histamine release in mast cells through the mechanism of inhibiting Ca^{++} influx. The results indicated that HC 20-511 inhibited 48/80-induced Ca^{++} influx dose-dependently, and that the inhibitory effects of HC 20-511 were greater than that in DSCG.

7. Dissociation of antianaphylactic and antihistaminic activities. Vol. 7, Page 216.

The purpose of this study was to determine whether HC 20-511's antianaphylactic and antihistaminic effects were interrelated. Following the administration of HC 20-511 in rats (1 mg/kg iv), the HC 20-511's antianaphylactic effect reached the peak at 8 min, and decreased thereafter and was only 15% inhibition after 4 hr. The antihistaminic effect was remained high (> 80%) for more than 4 hr. Two histamine antagonists, [redacted] (1.0 mg/kg, iv) and empyramine (5.6 mg/kg, iv), showed strong histaminic blocking effect, but failed to block passive cutaneous anaphylaxis. Combined administration of [redacted] and ketotifen produced additive antihistaminic effects, but no additive effects on passive cutaneous anaphylaxis were observed. The results suggested that ketotifen's antihistaminic and antianaphylactic effects might depend on 2 mechanisms. In in vitro study, ketotifen (10^{-6} to 3.2×10^{-4} M) did not inhibit antigen-induced histamine release from rat mast cells.

8. Inhibition of chemical mediator release from human leukocytes by HC 20-511 (ketotifen). Vol. 7, Page 228.

The purpose of this in vitro study was to explore theoretical background for using ketotifen in human beings. The results showed that HC 20-511 dose-dependently inhibited IgE-mediated release of both histamine and SRS-A from human basophils. 50% inhibition was reached at the concentrations around 100 µg/ml. The sponsor divided histamine release into 2 phases (an antigen-dependent, calcium-independent first phase and an antigen-independent, calcium-dependent second phase). In both phases, HC 20-511 exhibited inhibitory effect. HC 20-511 also inhibited SRS-A release from human neutrophils, while DSCG did not inhibit histamine and SRS-A release from basophils and neutrophils. The sponsor suggested that the mode of action between HC 20-511 and DSCG might be different.

9. Effects of cyproheptadine, ketotifen and sodium nitroprosside on mechanical activity and calcium uptake in guinea pig taenia coli in vitro. Vol. 7, Page 265.

The purpose of this study was to explore the effects of ketotifen on smooth muscle contraction. Ketotifen blocked guinea pig taenia coli smooth muscle contraction and calcium influx caused by sustained membrane depolarization, but spontaneous and spike-dependent contractions were not affected. The depolarization-induced smooth muscle contractions were involved in anaphylactic responses.

10. β-adrenergic tachyphylaxis in the rat and its reversal and prevention by ketotifen. Vol. 7, Page 278.

In this study, ketotifen's effects on tachyphylaxis of isoprenaline were investigated. The results indicated that ketotifen not only reversed isoprenaline's tachyphylaxis, but that in its presence, the development of tachyphylaxis was prevented.

11. Comparative pharmacological investigations with the (+) and (-) antipodes of HC 20-511 (34-145 and 34-146 respectively). Vol. 7, Page 338.

Several tests were conducted to compare the pharmacological effects of (+) and (-) anpitodes of ketotifen. No differences were noted in antianaphylactic and antihistaminic actions. The [redacted] and anticholinergic activities were attributed to (+) antipode.

12. Comparative pharmacological investigations with two metabolites of ketotifen, the N-oxide (21-829) and nor-ketotifen (21-830). Vol. 7, Page 349.

Several tests were conducted to compare the pharmacological effects of two metabolites of ketotifen. The antianaphylactic and antihistaminic activities were lower in the metabolites than in ketotifen. In acute intravenous toxicity study in mice, the LD_{50} of ketotifen, N-oxide and nor-ketotifen were 13.8 mg/kg, 35.2 mg/kg and 48.3 mg/kg, respectively.

13. Effects of ketotifen fumarate eye drops on experimental conjunctivitis in rats and guinea pigs. Vol. 8, Page 001.

The purpose of this study was to evaluate the effects of ketotifen fumarate ophthalmic solution on allergic and non-allergic conjunctivitis. In rats and guinea with IgE-mediated passive anaphylactic conjunctivitis, ketotifen eye drop dose-dependently inhibited dye leakage with ID_{50} of 0.19 (in rats) and 6.7 (in guinea pig) μg/eye, respectively. Histopathology examinations conducted in rats supported ketotifen's efficacy with respect to edema, cell infiltration and lymph duct dilation. In rats with 48/80-induced non-allergic conjunctivitis, ocular instillation of ketotifen suppressed the dye leakage with ID_{50} of 0.78 mg/eye. Intravenous injection of ketotifen (1 mg/kg) also showed strong inhibitions in these animal models.

14. Effects of [redacted]almide, naaxia, opticron, [redacted]DR 15015 and DR 15016 on ocular immediate hypersensitivity in the albino rat (compound 48/80 model). Vol. 8, Page 012.

The purpose of the study was to compare the effects of several compounds on experimentally induced immediate hypersensitivity in male rats. The allergic reactions were induced by instillation of compound 48/80 that induced a release of histamine and other allergy mediators from mast cells. Test substances were administered topically qid for 3 days before the induction of allergy. The blood-eyelids and blood-eyeballs Evans' blue permeability indexes were the major parameters to discriminate all treatment groups in this model. The results indicated that [redacted]was at least as effective as levocabastine (an approved H_1 receptor antagonist) in reducing allergic responses induced by 48/80.

15. Ketotifen and olopatadine. Effect on ocular immediate hypersensitivity in the albino rat (compound 48/80 model). Vol. 8, Page 055.

The effects of [redacted](ketotifen fumarate 0.025% eye drops) on ocular immediate hypersensitivity induced by 48/80 were compared with other compounds. The blood-eyelids and blood-eyeballs Evans' blue permeability indexes were the major parameters to discriminate all treatment groups in this model. The results showed that ketotifen fumarate 0.025% eye drops were more effective in reducing allergic response than Patanol™ and levocabastine 0.05% eye drops when considering reduction of blood to eyelids extravasation. For the reduction of blood to eyeballs extravasation, ketotifen, Patanol™ and levocabastine were equally potent.

16. Effect of [redacted]almide, naaxia, opticron, [redacted]DR 15015 and DR 15016 on ocular active anaphylaxis in the guinea pig (compound 48/80 model). Vol. 8, Page 093.

The purpose of the study was to evaluate the effects of several compounds on ocular active anaphylaxis in male guinea pigs. The allergic reactions were induced by immunization and challenge with ovalbumin. Test substances were administered topically qid for 3 days before the induction of allergy. The blood-eyelids and blood-eyeballs Evans' blue permeability indexes were the major parameters to discriminate all treatment groups in this model. The results indicated that [redacted](0.05% ketotifen fumarate) was at least as effective as Livostin™ in reducing allergic responses in eyelids and eyeballs.

17. Ketotifen and olopatadine. Effect on ocular active anaphylaxis in the guinea pig (compound 48/80 model). Vol. 8, Page 134.

The effects of [redacted](ketotifen fumarate 0.025% eye drops) on ocular anaphylaxis induced by immunization and challenge with ovalbumin were compared with Patanol™. Test substances were instilled topically into the right conjunctival sac qid for 3 days before the induction of allergy. The results showed that ketotifen fumarate 0.025%

eye drops were more effective in reducing allergic response than Patanol™ and Livostin™ when considering reduction of blood to eyelids and blood to eyeballs extravasation.

18. Effect of ketotifen and olopatadine on eosinophil infiltration into the guinea pig conjunctiva. NDA supplement submitted 4-30-99, Page 169.

The purpose of this study was to assess ketotifen's efficacy on conjunctival eosinophil inhibition that was related to the late-phase allergic reactions in the eyes. Male guinea pigs were sensitized to chicken egg albumin (ovalbumin). On the day of test, the guinea pigs were anaesthetized and ^{111}In-oxine labeled eosinophils (0.1 ml/100 g) were injected into the jugular vein. The test substances (ketotifen fumarate ophthalmic solution (0.025%) or Patanol) were applied topically to one eye (the other eye received saline). Hypersensitive reactions in the conjunctiva were induced by topical application of 10 µl of 5% ovalbumin solution (500 µg) to both eyes. The animals were sacrificed 2 hr later and radioactivity in the conjunctiva was determined with a γ counter. The results showed that both ketotifen and Patanol could inhibit eosinophil infiltration to the level of the unchallenged eyes. There was no significant difference between these 2 drugs.

Safety pharmacology

19. Cardiovascular activities. Vol. 7, Page 183.

A. Isolated, spontaneous-beating guinea-pig atrium

Epinephrine (2.5×10^{-6} M) induced an increase in the rate and force of contractions of guinea pig atrium preparations. The increase was inhibited by HC 20-511 (↓beating rate at 2×10^{-6} M and above; ↓contractile force at 5×10^{-5} M).

B. Influence on the functional refractory period (FRP) of isolated guinea-pig atrium

The results of the study using left atrium from albino guinea pigs indicated that HC 20-511 dose-dependently increased the FRP (at doses of 5×10^{-6}M to 5×10^{-5} M).

C. Antiarrhythmic activity in the mouse in vivo

HC 20-511 dose-dependently inhibited chloroform-induced ventricular fibrillation in mice with ED_{50} of 66 mg/kg, ip. At the highest dose (100 mg/kg ip), convulsions were noted in 60% of the mice.

D. Cardiovascular studies in the anesthetized cat

HC 20-511 had no significant cardiovascular effects on the anesthetized cats except at accumulated dose of 18.7 mg/kg iv, at which the drug inhibited isoproterenol-induced tachycardia and the carotid occlusion response. This study was reviewed by Dr.

Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 54.

E. Hemodynamic studies in the anaesthetized open chest dog

In this study, HC 20-511 (5 mg/kg iv) produced a mild increase in heart rate, contractile force, and aortic mean flow. The first 2 changes lasted for about 30 min while cardiac output fell slightly below the control values. One hr following the infusion, stroke volume decreased (15%), and blood pressure and total peripheral resistance increased (9% and 26%, respectively). No ECG changes were noted.

20. Renal actions. Vol. 7, Page 194.

A. Renal functions in the conscious rat

Subcutaneous administration of HC 20-511 (0.01-3 mg/kg) produced a slight decrease in urine production and electrolyte excretion. Oral administration (0.1-3 mg/kg) produced a decrease in urine production and Na^+ and Cl^- excretion, but K^+ concentration was increased. At 30 mg/kg po, HC 20-511 produced a marked increase in urine production and electrolyte excretion.

B. Renal actions in the conscious dog

The study was conducted in 5 trained male beagle dogs. Oral administration of HC 20-511 at 0.1 and 1 mg/kg reduced urine volume and Na^+ and Cl^- excretion, but K^+ concentration was increased. At 3 mg/kg, the drug showed similar effects except that the urine volume was unchanged.

21. Effects in CNS. Vol. 7, Page 199.

A. Primary observation test in the mouse

The study was conducted in mice. Each dose was given to 3 male animals (3-270 mg/kg), and the results (see table below) were compared with a control group.

The effects of HC 20-511 on CNS in mice

Dose (mg/kg)	3		10		30		90		270	
	po	sc	po	sc	po	sc	po	sc	po	sc
Locomotor activity	-	-	-	-	-	(↓)	(↓)	↓	-	↓
Behavior stimulated	-	-	-	-	(↑)	(↑)	↑	(↑)	-	↑
Behavior inhibited	-	-	-	-	-	(↓)	(↓)	↓	-	↓
Muscle tone	-	-	-	-	-	↓	-	↓	(↑)	↓
Neurological signs	-	-	-	-	-	+	-	+	(+)	+
Autonomic effects	-	-	-	-	-	-	-	-	(+)	-
Nociceptive responses	-	-	-	-	-	-	-	-	-	↓

↓ or ↑ decrease or increase compared to controls

() weak effect; + present; - no change

B. Climbing test in the mouse

This study was reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 54.

C. Tetrabenazine antagonism in the rat

Animals were treated with HC 20-511 30 min before administration of tetrabenazine (10 mg/kg, sc). Forty min later, the degree of catalepsy and ptosis were investigated in the animals. The results indicated that no significant effects on tetrabenazine-induced catalepsy and ptosis were observed.

Ancillary pharmacology

22. Local anaesthesia in the rat. Vol. 7, Page 202.

HC 20-511 dissolved in 0.9% saline was applied topically to the right eye of the male rats and the blink reflex was determined 2 min later. The results indicated that at the concentrations up to 3.2%, no local anaesthetic effects were noted.

23. The effects of ketotifen (HC 20-511 hfu) in the gross behavior in Cebus monkeys. Vol. 7, Page 304. [Reviewer's comment: "hfu" is hydrogen fumarate.]

This was a dose-ranging test for the following sleep pattern study. Two monkeys were orally dosed with ketotifen at escalating doses of 2.5, 5 or 10 mg/kg with a 6-day interval. One monkey was treated with the drug at 10 mg/kg. The animal that received only 10 mg/kg of ketotifen showed mild drug effects including slight increases in the frequency of micturition, slight diarrhea and tremors of mild intensity.

24. Evaluation of 20-511 on the sleep patterns of Cebus monkeys. Vol. 7, Page 317.

Ketotifen's effects on sleep profiles in 2 male monkeys implanted with chronic electrodes were evaluated. The monkeys were orally dosed with HC 20-511 at 0.5, 2, 4, 8 and 10 mg/kg with a 6-day interval. Significant sedative/hypnotic activity was noted in doses of 4-10 mg/kg in 1 animal.

25. Actions in immunopharmacological models. Vol. 7, Page 329.

The purpose of this study was to determine whether ketotifen had immunosuppressive properties. In mouse study, ketotifen (60 mg/kg iv or 90 mg/kg po) did not significantly influence the number of plaque-forming cells per spleen. In cell-mediated immunity study conducted in guinea pig, skin hypersensitivity was only slightly

inhibited by ketotifen (90-100 mg/kg, po). Although in one oxazolone skin test study in mice, ketotifen (90 mg/kg, po) decreased skin reaction significantly, the drug showed no effects in the second study. In in vitro study, ketotifen (10 µg/ml) showed no effects on the proliferation of mouse spleen lymphocytes induced by concanavalin. The results suggested that ketotifen is not an immunosuppressive agent.

Pharmacokinetics:

Reviewer's comment: All of the PK studies were submitted in [redacted]

Studies reviewed:

1. Ketotifen-^{14}C: absorption, blood levels, distribution and excretion in the mouse. Vol. 8, Page 2391.
2. Metabolic fate of ^{14}C-ketotifen fumarate in rats. Absorption, excretion and distribution after ophthalmic administration. Vol. 9, Page 3006.
3. ^{14}C-HC 20-511 (hfu), absorption in the rat from the drug-food mix. Vol. 8, Page 2428.
4. Plasma levels in rats after acute and chronic oral administration of HC 20-511. Vol. 8, Page 2441.
5. Resorption of bile metabolites of ^{3}H-HC 20-511 in the rat. Preliminary experiments. Vol. 8, Page 2505.
6. The pharmacokinetics of ^{14}C-HC 20-511 in rat, dog and rhesus monkey. Vol. 8, Page 2621.
7. Distribution of ^{14}C-ketotifen fumarate in rabbit eye tissue after ophthalmic administration. Vol. 9, Page 3015.
8. Distribution of ^{14}C-ketotifen fumarate in rabbit eye tissue after single and repeated doses of ophthalmic solution. Vol. 9, Page 3025.
9. Macroautoradiographic study of the distribution of ^{14}C HC 20-511 in male rats after single and chronic administration and in pregnant rats after a single dose. Vol. 8, Page 2516.
10. The pharmacokinetics of ^{3}H-HC 20-511 (-hfu) in rat, dog and monkey. Vol. 8, Page 2574.
11. Metabolism of ^{3}H- and ^{14}C-HC 20-511 in the rat. Vol. 8, Page 2455.
12. Metabolites of ^{14}C-HC-20-511 in plasma and some organs of the rat. Vol. 8, Page 2493
13. Estimation of N-demethylation of ^{14}C-HC 20-511 in rats and dogs. Vol. 8, Page 2540.
14. Comparison of ^{3}H-HC 20-511 biotransformation in rat, dog, rabbit, rhesus monkey and human. Vol. 8, Page 2683.
15. Metabolism of ^{3}H-HC 20-511 and ^{14}C-HC 20-511 in the dog. Vol. 8, Page 2735.
16. Metabolism of ^{3}H-HC 20-511 in the rabbit. Vol. 8, Page 2720.
17. Metabolism of ^{3}H-HC 20-511 in the rhesus monkey. Vol. 8, Page 2776.
18. Binding studies with blood cells and plasma proteins. Vol. 9, Page 2800.
19. Binding to blood cells and plasma proteins. Vol. 9, Page 2814.
20. Binding of ^{3}H-HC 20-511, ^{3}H-BC 105 and ^{3}H-HS 592 to serum proteins. Vol. 9, Page 2826.
21. Protein binding of ^{3}H-HC 20-511 to serum protein. Vol. 9, Page 2881.
22. Excretion of HC 20-511 in rat milk. Vol. 8, Page 2447.

Review:

Absorption Pharmacokinetics:

1. Ketotifen-^{14}C: absorption, blood levels, distribution and excretion in the mouse. Vol. 8, Page 2391.

Study Nº: DM-1-6/15/81
Compound: [redacted]
Route: Intravenous and oral
Dose Level: 1 mg/kg
Dosing Regimen: Single dose
Animal: Male CD-1 mice, 25 g, 3/group/time point. 25/group for excretion study.
GLP: No

The purpose of this study was to investigate the PK profile of ketotifen-^{14}C in mice following a single oral or iv administration. Blood and tissue samples were collected 0.2, 1, 6, 12, 24 and 72 hr following dosing. Additional blood samples were collected 0.083 (iv only), 2, 4, 8 and 48 hr following dosing. For excretion study, urine and feces samples were collected at regular intervals for 72 hr. Radioactivity was determined by liquid scintillation counting.

Results:

PK parameters and excretion data for this study are summarized in the following tables. After iv and po administrations, the tissues with the highest concentrations of radioactivity were liver, kidneys and lungs, while in brain the radioactivity concentrations were relatively low. The decline of the radioactivity was rapid and paralleled that of the blood concentration.

Blood PK parameters of ketotifen after a single iv or po administration in mice (n = 3)

Species	Dose	Sex	Tmax (hr)	Cmax (µg•eq/ml)	T1/2 (hr)	$AUC_{0-\infty}$ (µg-eq/ml)
Mouse	1 mg/kg po	♂	0.5	0.122	20	0.62
	1 mg/kg iv	♂	5 min	0.207	28	0.808

Excretion of radioactivity after a single dose (1 mg/kg) of Ketotifen-^{14}C in mice (n=25)

	Oral		Intravenous	
Time interval (hr)	Urinary excretion	Fecal excretion	Urinary excretion	Fecal excretion
0-12	21.07 ± 4.78	53.08 ± 14.54	23.14 ± 1.63	57.09 ± 9.74
12-24	3.53 ± 0.58	12.07 ± 5.97	2.30 ± 0.23	8.16 ± 4.44
24-48	1.05 ± 0.25	1.71 ± 1.13	0.93 ± 0.15	1.14 ± 0.22
48-72	0.33 ± 0.16	0.41 ± 0.08	0.46 ± 0.34	0.56 ± 0.13
Subtotal	25.98 ± 5.10	67.27 ± 14.09	26.84 ± 1.70	66.94 ± 6.93
Total	94.98 ± 9.73		94.40 ± 8.04	

2. Metabolic fate of ^{14}C-ketotifen fumarate in rats. Absorption, excretion and distribution after ophthalmic administration. Vol. 9, Page 3006.

Study Nº: Not indicated
Compound: ^{14}C-HC 20-511
Route: Ocular, Topical
Dose Level: 10 µl (100 µg), right eye only
Dosing Regimen: Single dose
Animal: Male Wistar rats, 8 weeks old, 302 ± 3 g
GLP: No

The purpose of this study was to determine the blood concentration, urinary and fecal excretion, and in vivo distribution of ketotifen fumarate after ocular instillation in rats. Blood samples were collected 15, 30 and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96 and 120 hr after dosing. Urinary and fecal samples were collected 6, 12, 24, 48, 72, 96 and 120 hr after dosing. Radioactivity was measured by a Designated rats were sacrificed 15 and 45 min, and 4 and 24 hr after administration and in vivo distribution was determined by autoradiograms.

Results:

The results from blood concentration, urinary and fecal excretion tests are summarized in the tables below. Regarding in vivo tissue distribution, high radioactivity was detected in eyeball and surrounding area, nasal cavity, oral cavity, gastrointestinal contents, liver, lungs, kidneys, spleen and submaxillary glands.

PK parameters following ocular administration of ketotifen fumarate to rats

Dose	Tmax (hr)	Cmax (ng-eq/ml)	T1/2 α (hr)	T1/2 β (hr)
100 µg/eye	0.75	16.3	3	43

Cumulative excretion of radioactivity after ocular dosing to rats (% of dose)

Time (hr)	Urine	Feces	Total
24	6.99 ± 0.47	56.51 ± 1.22	63.50 ± 1.04
48	8.49 ± 0.51	75.90 ± 1.87	84.39 ± 1.82
72	9.01 ± 0.54	80.10 ± 1.81	89.10 ± 1.62
120	9.78 ± 0.53	83.28 ± 1.57	93.06 ± 1.21

3. ^{14}C-HC 20-511 (hfu), Absorption in the rat from the drug-food mix. Vol. 8, Page 2428.

The purpose of this study was to determine quantitatively the absorption and excretion of ^{14}C-HC 20-511 when dosed with food in rats (1 mg/kg and 10 mg/kg). The results indicated that about 90% of the drug was absorbed as a drug-food mix, 65-72% of the radioactivity was excreted in bile, and that the onset and the rate of absorption were slower than that from an aqueous solution. For detailed information, please reference Pharmacology Review Amendment dated September 30, 1978 (Attachment 3), Page 7.

4. Plasma levels in rats after acute and chronic oral administration of HC 20-511. Vol. 8, Page 2441.

The purpose of this study was to determine if the drug was well absorbed and if there was a clear correlation between the doses and the maximum plasma levels after long term treatment. The results indicated that the drug was well absorbed after long-term treatment, and that the Cmax values of the drug plus nor 20-511 at mid and low doses given by stomach tube and in the diet were comparable. For detailed information, please reference Pharmacology Review [redacted] Amendment dated September 30, 1978 (Attachment 3), Page 9.

5. Reabsorption of bile metabolites of ^{3}H-HC 20-511 in the rat. Preliminary experiments. Vol. 8, Page 2505.

Study N^{o}: Not indicated
Compound: ^{3}H-HC 20-511[redacted]
Route: Oral
Dose Level: 1 mg, first rat
Dosing Regimen: Single dose
Animal: Rats
GLP: No

The purpose of this study was to determine the reabsorption of HC 20-511 and its metabolites using cascaded biliary fistula rats, in which the biliary fistula from the first rat was connected to the duodenum of the second rat. The fistula of the second rat was used to collect bile. The urine and bile were collected at 0-24 hr, 24-48 hr, and 48-72 hr intervals.

Results:

The table below shows that enterohepatic circulation for HC 20-511 and its metabolites existed in rats. At least 1/3 of the radioactivity was reabsorbed and eliminated in the second rat.

Excretion of ^{3}H-radioactivity in urine and bile of the second rat after oral dosing of 1 mg of ^{3}H-HC 20-511 to the first rat

% of dose	Rat 1		Rat 2	
Time (hr)	Bile	Urine	Bile	Urine
0-24	17.5	0.71	20.8	0.78
24-48	7.4	1.4	10.1	1.9
48-72	2.5	0.8	2.2	-
Total	30.3		35.8	

6. The pharmacokinetics of ^{14}C-HC 20-511 in rat, dog and rhesus monkey. Vol. 8, Page 2621.

Study N^{o}: Not indicated

Compound: ^{14}C-HC 20-511

Dosing Regimen: Single dose

Dose and Route:

Species	Dosage (mg/kg)	
	iv	po
Rat	1.0	1.0
Dog	0.5	0.5
Monkey	0.5	0.5

Animal: Wistar rats, 200-260 g, 3/sex/group; beagle dogs, 11-12.5 kg, 1 ♀, 2♂; rhesus monkeys, 8-11 kg, 3♂

GLP: No

The purpose of this study was to investigate the pharmacokinetics of ketotifen in rats, dogs and monkeys. Blood, urine, feces and bile samples were collected at the designated time points. were used in this study.

Results:

In all of the 3 species, ketotifen was well absorbed. Plasma PK parameters are summarized in the table below. In tissue distribution test in rats, lungs, liver and kidneys showed high levels of radioactivity. Excretion data are presented in the second table below.

Plasma PK parameters following iv or po administrations of Ketotifen

Species	Intravenous				Oral			
Dose (mg/kg)	Cmax(µg-eq/ml)	Tmax (hr)	T1/2 (hr)	AUC (µg-eq•hr/ml)	Cmax(µg-eq/ml)	Tmax (hr)	T1/2 (hr)	AUC (µg-eq•hr/ml)
Rat ♂	0.167	0.2	20	1.287	0.110	2	36	1.180
1	±0.024			±0.159	±0.032			±0.107
Rat ♀	0.199	0.2		1.516	0.075	2		1.312
1	±0.006			±0.219	±0.032			±0.030
Dog	0.150	0.05	67	2.638	0.181	2	206	3.947
0.5	±0.049			±0.399	±0.085			±0.041
Monkey	0.138	5	33	4.872	0.110	7	45	2.974
0.5	±0.035			±1.060	Not avail.			±0.607

Excretion of ^{14}C-activity with urine and feces in rats, dogs and monkeys (% of doses)

Species	Intravenous			Oral		
0-96 hr	Urine	Feces	Total	Urine	Feces	Total
Rat*	13.0 ± 1.2	82.9 ± 10.2	96.0 ± 9.7	10.4 ± 1.5	94.0 ± 9.2	104.5 ± 10.0
1 mg/kg						
Dog	31.5 ± 5.8	52.8 ± 9.7	84.3 ± 3.9	38.6 ± 9.2	65.9 ± 3.7	103.5 ± 12.9
0.5 mg/kg						
Monkey	40.5 ± 6.5	53.5 ± 19.3	94.0 ± 22.9	53.9 ± 6.4	43.2 ± 14.0	97.1 ± 7.6
0.5 mg/kg						

* 0-168 hr

Distribution:

7. Distribution of ^{14}C-ketotifen fumarate in rabbit eye tissue after ophthalmic administration. Vol. 9, Page 3015.

Study No: Not indicated
Compound: ^{14}C-ketotifen fumarate ophthalmic solution
Animals: Male New Zealand white rabbits, 2.0-2.4 kg, 3/time point
Dose Level: 50 µl (0.5 mg), left eye only
Dosing Regimen: Single dose

The purpose of this study was to determine the ocular distribution of ketotifen after ocular topical administration. Ocular tissue and blood samples were collected 15, 30, 45 min, and 1, 2, 3, 4, 6, 8 and 24 hr after dosing. Radioactivity was determined by

Results:

The ocular tissue distribution and plasma PK parameters are listed in the tables below. The radioactivity concentrations in vitreous body, retina and chroid, and aqueous humor were low. The concentrations in the untreated eye were also low.

Ocular tissue distribution of ketotifen following a single ocular administration (µg-eq/g)

Time (hr)	0.25	0.5	1	2	4	6	8	24
Conjunctiva	37.7±15	7.8±0.9	3.5±1.0	0.5±0.1	0.6±0.2	0.4±0.05	0.3±0.02	0.4±0.2
Ant. sclera	20.8±2.3	6.6±1.9	2.6±0.6	0.3±0.03	0.3±0.06	0.2±0.03	0.1±0.02	0.1±0.05
Cornea epit.	77.3±18.9	22.9±7.6	12.7±4.3	1.5±0.14	0.8±0.16	1.3±0.23	0.5±0.05	0.95±0.23
Cornea	28.8±7.2	10.8±4.0	8.5±4.5	0.5±0.07	0.34±0.05	0.32±0.05	0.08±0.01	0.14±0.03
Iris	20.9±5.7	9.5±3.4	5.7±2.2	0.4±0.08	0.2±0.02	0.09±0.02	nd	0.03±0.01
Ciliary body	9.0±1.8	3.9±0.9	1.6±0.3	0.2±0.03	0.08±0.02	0.04±0.01	nd	nd
Plasma	0.039±0.002	0.058±0.009	0.087±0.031	0.084±0.018	0.044±0.009	0.013±0.003	0.013±0.001	nd
Liver	0.28±0.07	0.5±0.05	0.6±0.09	0.5±0.02	0.38±0.01	0.2±0.008	0.15±0.02	0.06±0.016

Nd: not detected (<20dpm)

PK parameter in plasma and ocular tissues

	Cmax(µg-eq/ml)	Tmax (hr)	T1/2 (hr)	AUC (µg-eq hr/ml)
Plasma	0.087	1	1.475	0.366
Cornea (epithelia)	77.3	0.25	2.615	60.18
Cornea	28.8	0.25	2.624	22.39
Conjunctiva	37.7	0.25	10.67	24.15
Iris	20.9	0.25	11.77	18.90
Anterior sclera	20.8	0.25	3.556	15.93

8. Distribution of ^{14}C-ketotifen fumarate in rabbit eye tissue after single and repeated doses of ophthalmic solution. Vol. 9, Page 3025.

Test N^{o}: SK-8901

Animal: Male New Zealand white rabbits, 2-2.5 kg, 3/group
Compound: ^{14}C-ketotifen fumarate ophthalmic solution
Route: Ocular, topical
Dose Level: 9.01 µCi/0.5 mg/50 µl (for single dose) and 9.98 µCi/0.5 mg/50 µl (for multiple doses)
Dosing Regimen: Single or 2 and 17 doses (The sponsor did not provide information about dosing interval.)
Time of Sampling:

Group	Sampling time
Single dose	15 and 30 min, and 1, 3, 6 and 24 hr after administration
2 administrations	15 min and 6 hr after the final administration
14 and 17 administrations	Prior to the 14th dosing and 30 min, 1 hr and 6 hr after the final dosing

GLP: No

The purpose of this study was to determine the ocular distribution of ketotifen fumarate ophthalmic solution following single and repeated administrations in rabbits. Radioactivity was measured by a [redacted]

Results:

The distribution of the drug in ocular tissues following a single dose is summarized in the table below. Cornea, bulbar conjunctiva, lower conjunctiva and iris had high levels of radioactivity at 15 min. The concentrations decreased rapidly. Plasma radioactivity was noted at 15 min and peaked at 1 hr. Comparison between the single and multiple administrations is listed in the second table.

Ocular tissue distribution of ketotifen ophthalmic solution after a single dose (µg-eq/g)

Time	15 min	30 min	1 hr	3 hr	6 hr	24 hr	$AUC_{0-\infty}$ (µg-eq/ml)
Cornea	41.327±15.61	7.217±2.14	5.823±2.7	1.793±0.30	1.186±0.427	0.535±0.086	51.58±9.8
Bulbar conjunctiva	8.512±3.65	4.326±0.41	3.021±1.63	0.924±0.43	0.669±0.28	0.145±0.08	20.47±2.4
Upper conjunctiva	3.773±0.64	1.673±0.73	1.589±1.57	1.258±0.42	0.309±0.08	0.061±0.02	10.96±2.5
Lower conjunctiva	13.337±10.60	4.775±3.775	3.981±4.02	1.866±1.16	0.525±0.19	0.158±0.08	22.98±14.3
Iris	27.05±9.03	4.507±2.13	2.341±0.67	0.446±0.14	0.165±0.07	0.073±0.03	15.67±3.0
Sclera	5.248±1.41	0.943±0.13	0.786±0.19	0.273±0.09	0.157±0.07	0.162±0.06	12.11±6.3
Aqueous humor	2.692±1.00	0.491±0.14	0.319±0.03	0.053±0.02	0.036±0.01	0.009±0.003	1.96±0.18
Plasma	0.039±0.01	0.064±0.02	0.096±0.01	0.079±0.02	0.034±0.01	0.006±0.003	0.82±0.12

Comparison of radioactivity concentrations between single and multiple administrations

Time	15 min	6 hr	6 hr	6 hr	30 min	1 hr
Dose group	2 doses/single dose	2 doses/single dose	13 doses/single dose	17 doses/single dose	17 doses/single dose	17 doses/single dose
Cornea	1.09	2.43	3.79	4.13	2.8	1.53
Bulbar conjunctiva	1.12	1.95	3.69	3.22	2.0	0.84
Upper conjunctiva	1.11	3.44	8.96	6.54	3.57	1.92

Time	15 min	6 hr	6 hr	6 hr	30 min	1 hr
Dose group	2 doses/single dose	2 doses/single dose	13 doses/single dose	17 doses/single dose	17 doses/single dose	17 doses/single dose
Lower conjunctiva	1.02	7.37	10.78	8.78	4.95	1.69
Iris	1.00	4.59	6.16	5.44	1.09	1.01
Sclera	1.07	1.59	5.57	5.59	2.53	1.43
Aqueous humor	1.05	1.86	1.86	2.67	1.07	0.98
Plasma	2.28	1.29	1.79	2	2.02	1.33

9. [redacted] study of the distribution of ^{14}C HC 20-511 in male rats after single and chronic administration and in pregnant rats after a single dose. Vol. 8, Page 2516.

Study Nº: Not indicated
Compound: ^{14}C-HC 20-511 [redacted]
Route: Oral
Dose Level: 1 mg/kg
Dosing Regimen: Single dose or qd x 8 days
Time of Sampling: In single dose treatment, 0.5, 2, 8, 24 and 48 hr after single dosing; In multiple treatment, 8, 24 and 48 hr after the last administration.
Animal: Wistar rats, 170-190 g for males, 350-400 g for pregnant rats
GLP: No

The purpose of this study was to determine the distribution pattern of the drug under different conditions. Autoradiography [redacted] and thin layer chromatography (TLC) were used in this study.

Results:

HC 20-511 was absorbed rapidly. Liver, lungs and kidneys were found to have high levels of radioactivity. No differences in drug distribution were found between single and multiple treatments. No drug accumulation was noted. The drug could pass the placental barrier easily, which was evidenced by radioactivity in the fetal intestinal tract. With respect to excretion, about 80-95% of the radioactivity was eliminated in feces, and 5-7% in urine. In urine, almost no parent drug was excreted, and the main metabolite was nor HC 20-511.

10. The pharmacokinetics of ^{3}H-HC 20-511 (-hfu) in rat, dog and monkey. Vol. 8, Page 2574.

This study was reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 42.

In distribution test, the liver, lungs and kidneys were shown to have high levels of radioactivity. In addition, very high concentration of radioactivity was found in the gall bladder in dog study.

Excretion of ^{3}H-radioactivity in urine and feces after iv and oral administration (% of dose)

Species	Time (hr)	Intravenous			Oral		
Rat		Urine	Feces	Bile	Urine	Feces	Bile
1 mg/kg	0-24	7.9 ± 0.2	52.2 ± 5.6	72.9 ± 1.7	6.4 ± 0.2	53.9 ± 4.1	71.6 ± 4.2
	0-48	9.4 ± 0.3	76.3 ± 2.5	74.6 ± 1.6	7.7 ± 0.4	82.2 ± 3.8	75.6 ± 4.1
	0-72	10.0 ± 0.3	84.0 ± 1.5		8.4 ± 0.4	88.0 ± 2.4	
	0-96	10.4 ± 0.3	85.0 ± 1.7		8.8 ± 0.4	88.9 ± 2.1	
Dog		0.05 mg/kg			5.0 mg/kg		
	0-24	27.9 ± 5.6	24.6 ± 15.8		30.0 ± 1.1	31.4 ± 2.0	
	0-48	30.6 ± 6.0	45.4 ± 7.8		31.9 ± 0.8	44.4 ± 4.2	
	0-72	31.5 ± 6.1	51.4		32.5 ± 0.8	46.2 ± 3.7	
	0-102		47.6			46.6 ± 3.8	
	0-168	33.5 ± 6.2	51.8 ± 4.9		33.8 ± 1.0	46.9 ± 3.8	
		0.5 mg/kg					
	0-24	29.3 ± 5.2	31.1 ± 3.7		22.3 ± 9.9	--	
	0-48	32.2 ± 4.4	38.7 ± 5.0		28.7 ± 6.5	41.6 ± 7.3	
	0-72	32.9 ± 4.2	41.9 ± 2.4		30.0 ± 7.0	--	
	0-96	33.5 ± 4.3	42.7 ± 2.9		30.3 ± 6.9	47.3 ± 4.0	
	0-168	34.9 ± 4.3	43.3 ± 2.9		31.4 ± 7.0	49.9 ± 5.6	
Monkey		Urine	Feces	Urine	Feces	Urine	Feces
Oral		0.38 mg/kg				4.9 mg/kg	
	0-24	30.1	33.0			30.3	3.7
	0-48	33.8	39.9			34.1	32.5
	0-72	34.7	41.3			35.1	38.7
	0-96	35.3	42.1			35.7	40.4
	0-167	36.5				37.0	41.3
iv		0.05 mg/kg		0.5 mg/kg		1.0 mg/kg	
	0-24	28.7		32.5	18.8	33.8	15.2
	0-48	38.1	23.7	37.3		37.8	35.7
	0-72	39.5	37.5	38.7	38.1	39.8	40.8
	0-96	40.5	42.4	39.6	40.4	40.9	41.8
	0-167	42.3	44.1	41.0	42.1	42.6	43.1

Metabolism:

11. Metabolism of ^{3}H- and ^{14}C-HC 20-511 in the rat. Vol. 8, Page 2455.

Study Nº: Not indicated
Compound: [redacted]C-HC 20-511
Animal: Male Wistar rats
The following table summarizes the purpose and dose for each test.

Purpose of test	Dose (mg/kg, po)	Sample collected
Metabolic pattern (low dose)	1	Urine and bile, 0-24 hr
Metabolic pattern (high dose)	50	Urine and bile, 0-24 hr
Metabolic pattern at Day 4	50 x 4 days	Urine, 0-24 hr
Metabolic pattern in blood	5	Blood, 1, 2, 4, 8 and 72 hr after dosing
Demethylation	1.5	Urine and feces, 0-72 hr
Reabsorption in the gut	1	Urine and bile of second animal, 0-72 hr
Preparative work	100	Urine

GLP: No

Results:

In the urine of the rats receiving 100 mg/kg of HC 20-511, 2 metabolites were discovered in addition to the parent compound: nor 20-511 and nor 20-511 carrying an ethylcyano side chain.

In the rats treated with HC 20-511 at 1 mg/kg and 50 mg/kg, the main excretion products in bile and urine were the parent compound and nor 20-511. Nor 20-511 was a main metabolite in urine. In the same rats, excretion of the drug by bile (67-69%) was more important than by urine (6-17%). Other tests also supported this finding. Plasma analysis indicated that soon after oral dosing, nor 20-511 appeared and was the largest part of the total radioactivity.

The methyl group of the ketotifen may be necessary for the antihistaminic activity. The test showed that 70% of the drug was demethylated in rats.

In the cascade fistula rats, it was found that about 30% of the dose was reabsorbed after the first biliary excretion.

12. Metabolites of ^{14}C-HC-20-511 in plasma and some organs of the rat. Vol. 8, Page 2493.

Study N°: Not indicated
Compound: ^{14}C-HC 20-511
Route: Oral
Dose: 2.1 mg/kg
Time of sampling: 5 min, 1, 3, 6 and 24 hr after dosing
Animal: Rats, about 317 g, 3/time point
GLP: No

The purpose of this study was to determine quantitatively the amount of HC 20-511 and its major metabolite, nor HC 20-511 in rats. were performed in this study.

Results:

The table shows the quantitation of HC 20-511 and nor HC 20-511 in plasma and several organs. In brain and plasma the drug and metabolite levels were much lower than in lungs and liver. The metabolite, nor HC 20-511 appeared soon after dosing.

Quantitation of HC 20-511 and nor HC 20-511 in plasma and several organs from rats treated with ^{14}C-HC 20-511 (2.1 mg/kg, po) ng/g

Time (hr)	Plasma		Brain		Lung		Liver	
	HC 20-511	Nor HC 20-511	HC 20-511	Nor HC 20-511	HC 20-511	Nor HC 20-511	HC 20-511	Nor HC 20-511
0.25	1.05	Trace	5.2	1.11	450	95	10200	18800
1	5.04	17.4	27.1	69	200	5600	8300	60000
3	Trace	19.7	22.8	85	140	8550	6000	40900
6	Trace	15.2	12.6	57	140	7100	3500	40000
24	trace	2.77	trace	14.5	trace	980	390	7600

13. Estimation of N-demethylation of ^{14}C-HC 20-511 in rats and dogs. Vol. 8, Page 2540.

Study N^{o}: Not indicated
Compound: ^{14}C-HC 20-511 [redacted]
Route: Oral
Dose Level: 1.5 mg/kg
Dosing Regimen: Single dose
Animal: Dogs and rats
GLP: No

The purpose of this study was to provide metabolic information on N-demethylation of HC 20-511. Urine and feces samples were collected at 0-24 hr, 24-48 hr and 48-72 hr intervals. The ratio of (^{3}H – ^{14}C)/^{3}H indicated the degree of demethylation.

Results:

The table below shows that among the total radioactivity, about 70% in rats and 39-45% in dogs was demethylated product. TLC test conducted in rats confirmed that the demethylated product was nor-HC 20-511.

Excreted ^{14}C- and ^{3}H-radioactivity in the urine and feces of rats and dogs treated with ^{14}C- and ^{3}H-HC 20-511 at 1.5 mg/kg, po (% of the dose)

Rats (n=5)	Urine ^{3}H	Feces ^{3}H	Total ^{3}H	Urine ^{14}C	Feces ^{14}C	Total ^{14}C	(^{3}H -^{14}C)/ ^{3}H
(0-72 hr)							
	8.3	58.7	67	4.2	17.2	21.4	68
Dog 1							
0-24 hr	18	50.2	68.2	12.3	27.5	39.8	41
24-48 hr	19*		19	7.8*		7.8	59
Total (0-48 hr)			87.2			47.6	45
Dog 2							
0-24 hr	12.6	40.4	53	8.9	25	33.9	36
24-48 hr	1.8	9.6	11.4	0.74	4.4	5.14	55
Total (0-48 hr)	14.4	50.0	64.4	9.64	29.4	39.0	39

14. Comparison of ^{3}H-HC 20-511 biotransformation in rat, dog, rabbit, rhesus monkey and human. Vol. 8, Page 2683.

This report, summarizing previously performed studies, compared biotransformation of HC 20-511 in several species. The following tables show the metabolites identified in different species. In human, parent drug glucuronide (7,8) was found in urine, which could be hydrolyzed to the parent drug. Other constituents in small amounts included parent drug (2), N-oxide (13, 14) and nor 20-511 (3, 4).

Metabolites identified in urine and bile samples from different species

Metabolite #	Description	Man	Dog	Monkey	Rabbit	Rat
2	Parent drug		+	+	-	+
3, 4	Nor 20-511		+	+	-	+
5	Nor 20-511 sulfate		+	+	+	-
7, 8	Glucuronide of HC 20-511		-	+	+	-
9, 10	Hydroxylamine glucuronides of nor 20-511		+	+	-	+
11, 11a	Tautomeric rearrangement products of 2-OH		-	+	-	-
12	Thiophene metabolites		+	+	-	-
13, 14	N-oxide		+	+	-	+
15	Amide of 11a		-	+	-	-
16			+	-	-	-
17			+	-	-	-
18			+	-	-	-
19			+	-	-	-
20			+	-	-	-
21			+	-	-	-
22			+	-	-	-
23			+	-	-	-
24			+	-	-	-

The Numbers represented different metabolites of ketotifen.

Relative amounts of urinary metabolites in man and animals after oral dose of ^{3}H-HC 20-511 (% radioactivity in urine)

Metabolite #	Man	Monkey 1	Monkey 2	Dog 1	Dog 2	Rat 1	Rat 2	Rabbit
2		5.0	2.0	13.6	6.9	-	0.2	-
3, 4		19.6	9.7	2.4	0.4	38.3	65.4	-
5		7.2	2.6	2.9	2.9	-	-	33.9
7, 8			4.3	-	-	-	-	28.6
9, 10		11.5	14.7	8.8	10.4	1.4	2.6	-
11		-	-	-	-	-	-	-
12		±	-	-	-	-	-	-
13, 14		1.2	4.0	30.9	38.3	6.0	6.6	-
20		-	-	11.5	15.1	-	-	-
23		-	-	+	+	-	-	-
24		-	-	+	+	-	-	-
Total		44.5	37.3	70.1	73.7	45.7	74.8	62.5

15. Metabolism of ^{3}H-HC 20-511 and ^{14}C-HC 20-511 in the dog. Vol. 8, Page 2735.

Study N^{o}: Not indicated

Compound: [redacted] ^{14}C-HC 20-511

Route: Oral
Dose Level: 1 mg/kg and 20 mg/kg
Dosing Regimen: Single dose
Animal: Basset dogs
GLP: No

The purpose of this study was to explore the metabolites of HC 20-511 in dogs. Urine, feces and plasma samples were collected. HPLC, [redacted] and TLC were performed in this study.

Results:

The metabolites found in dog urine under high dose (20 mg/kg) and low dose (1 mg/kg) are summarized in the table below. The main metabolite was N-oxide (13, 14). Metabolites 10 and 20 were not seen or lower in high dose urine, in which more parent drug was excreted. Demethylation data are presented in Study 13 of the PK section. Plasma drug distribution is listed in the second table below.

Metabolites of HC 20-511 in dog urine after oral dosing of 1 mg/kg and 20 mg/kg of ^{3}H-HC 20-511 in dogs (% of urine calculation)

Species	Metabolite	20 mg/kg	1 mg/kg
Dog	18, 19	3.225	5.15
	20	2.05	13.3
	23, 24	6.525	(Mainly 20)
	21, 22	4.55	4.8
	11	2.475	2.35
	16	2.775	
	17	2.075	2.9
	13, 14	48.3	36.7
	Parent drug	23.05	10.1
	3, 4	1.1	1.3
	10		9.6

Plasma drug and metabolites distribution in dogs treated orally with HC 20-511 (1 mg/kg)

Time of sampling	DPM/ml	% Extracted	Parent drug (%)	Nor metabolites (%)	N-oxide (%)	Polar met(%)
1 hr	149400	70	19	2	7	48
3 hr	141700	60	13	3	7	71
6 hr	71140	56	19	4	7	63
24 hr	77620		14	7	trace	71

16. Metabolism of ^{3}H-HC 20-511 in the rabbit. Vol. 8, Page 2720.

Study N^{o}: Not indicated
Compound: ^{3}H-HC 20-511 [redacted]
Route: Oral
Dose Level and Dosing Regimen: 0.8 mg/kg for Single dose and 50 mg/kg, qd x 4 days
Animal: Male rabbits, 2.5 kg
GLP: No

The purpose of this study was to explore the metabolites of HC 20-511 in rabbits. Urine samples were collected. HPLC was used in this study.

Results:

Animals treated with low dose (0.8 mg/kg) and high dose (50 mg/kg) showed no differences in metabolic profiles in urine. One major metabolite detected was nor 20-511 N-sulfate (5). Two minor metabolites (1 and 6) and small amount of HC 20-511 were also detected in rabbits' urine.

17. Metabolism of ^{3}H-HC 20-511 in the rhesus monkey. Vol. 8, Page 2776.

Study N^{o}: Not indicated
Compound: ^{3}H-HC 20-511 [redacted]
Route: Oral
Dosing Regimen: Single dose for 1 mg/kg and 5 mg qd x 2 days for 20 mg/kg
Animal: Rhesus monkeys
GLP: No

The purpose of this study was to explore the metabolites of HC 20-511 in monkeys. Urine samples were collected. HPLC [redacted] and TLC techniques were used in this study.

Results:

35% of the administered dose was excreted in urine in the first 24 hr. The metabolites detected in monkey urine are summarized in the table below. Demethylation was the major metabolic degradation pathway.

Metabolites of HC 20-511 detected in monkey urine

Species	Compound	Description
Monkey	2	Parent drug
	3, 4	Nor 20-511
	7, 8	Glucuronide of HC 20-511
	9, 10	Hydroxylamine glucuronides of nor 20-511
	5	Nor 20-511 sulphamate
	13, 14	N-oxide
	11a	Tautomeric rearrangement products of 2-OH
	12	Thiophene metabolites
	15	Amide of 11a

Protein binding studies:

18. Binding studies with blood cells and plasma proteins. Vol. 9, Page 2800.

The purpose of this in vitro study was to determine the plasma and blood distribution of HC 20-511 in human, bovine and rat in the concentration range of 0.1-200 µg/ml. The binding was studies by equilibrium dialysis.

Results:

The human serum protein binding of the drug was 75%. The uptake of the drug by erythrocytes was 80% in man and rat, 71% in cattle. The binding of the drug to both RBC and plasma proteins was concentration-independent. The bound fraction in human albumin was very low, indicating that other proteins were involved in the binding of HC 20-511 to human serum proteins. The tables below show the drug distribution in whole blood and plasma. The sponsor attributed the discrepancy between the free fraction in human serum and plasma to the human blood having been stored too long.

Distribution of HC 20-511 in whole blood

Species	Blood concentr. (µg/ml)	155	73.2	37.3	9.20	4.57	0.77	0.38	0.08
Human									
Rat	Blood concentr. (µg/ml)	159	80.1	39.6	9.54	4.82	0.83	0.41	0.09
	% plasma water	16	15	15	14	13	14	14	14
	% plasma proteins	22	23	23	25	26	28	27	28
	% blood cells	62	62	62	61	61	58	59	58
Bovine	Blood concentr. (µg/ml)	144	79.6	40.3	10.6	5.37	0.85	0.44	0.08
	% plasma water	18	17	16	16	15	14	14	14
	% plasma proteins	34	36	38	40	40	43	42	47
	% blood cells	48	47	46	44	45	43	44	39

Plasma protein binding of HC 20-511

Species									
Human									
Plasma									
Serum									
Rat	Total concentration (µg/ml)	148	67.9	34.4	8.9	4.23	0.80	0.40	0.09
	% binding	65	66	69	71	71	74	75	76
Cattle	Total concentration (µg/ml)	148	74.8	37.4	8.86	4.36	0.80	0.40	0.09
	% binding	75	76	77	80	80	81	81	81

19. Binding to blood cells and plasma proteins. Vol. 9, Page 2814.

The purpose of this in vitro study was to determine the plasma and blood distribution of HC 20-511 in human, cattle and rat in the concentration range of 0.1-200 µg/ml. The binding was studies by equilibrium dialysis.

Results:

The results obtained from the whole blood drug distribution test were similar to those list in Study 18, which showed that 40-70% of HC 20-511 was taken up by RBC. The results of the drug binding in whole blood, diluted RBC, plasma and serum are listed in the following table. The results were dose-independent, and similar to those presented

in Study 18. Also, the sponsor attributed the discrepancy between serum and plasma to the human blood having been stored too long.

Percent of FREE HC 20-511 in whole blood, diluted RBC, plasma and serum

Species									
Human	Whole blood								
Rat	Whole blood								
	Total concentration (µg/ml)	159	80.1	39.6	9.54	4.82	0.83	0.41	0.09
	% free	29	27	27	26	24	25	25	25
	Diluted RBC								
	Total concentration (µg/ml)	147	72.7	36.6	8.92	4.51	0.76	0.39	0.08
	% free	42	40	39	39	37	36	34	32
	Plasma								
	Total concentration (µg/ml)	148	67.9	34.4	8.90	4.23	0.80	0.40	0.07
	% free	35	34	31	29	29	26	25	24
Bovine	Whole blood								
	Total concentration (µg/ml)	144	79.6	40.3	10.6	5.37	0.85	0.44	0.08
	% free	27	25	24	23	22	21	21	21
	Diluted RBC								
	Total concentration (µg/ml)	136	66.7	33.1	7.84	3.99	0.74	0.38	0.07
	% free	48	46	46	42	40	40	39	38
	Plasma								
	Total concentration (µg/ml)	148	74.8	37.4	8.86	4.36	0.80	0.40	0.09
	% free	25	24	23	20	20	19	19	19

20. Binding of ^{3}H-HC 20-511, ^{3}H-BC 105 and ^{3}H-HS 592 to serum proteins. Vol. 9, Page 2826.

21. Protein binding of ^{3}H-HC 20-511 to serum protein. Vol. 9, Page 2881.

The purpose of these in vitro studies was to compare the plasma binding of HC 20-511, BC 105 and HS 592 in the concentration range of 10-200 µg/ml. The binding was studies by dialysis and ultracentrifugation. **[Reviewer's comment:** Only HC 20-511 is reviewed.]

Results:

The following table compares the degree of binding of HC 20-511 in various sera. K values represent the total association constant, indicating the binding affinity of a compound to a given animal serum. Human serum had the highest binding affinity. Since human and bovine albumin solutions showed very low binding power (K = -0.02 and -

0.04), it could be concluded that albumin was not the only component of the serum to bind to HC 20-511.

K values of various sera

K	Human	Rabbit	Guinea pig	Cat	Dog	Monkey	Rat
Avg. protein binding (%)		82.24	81.1	77.5	78.7	78	73.6
HC 20-511		0.66	0.68	0.56	0.55	0.55	0.35

Excretion in milk:

22. Excretion of HC 20-511 in rat milk. Vol. 8, Page 2447.

The purpose of this study was to investigate whether ketotifen passed into the breast milk after oral administration to lactating rats. Eight lactating rats were orally dosed with ^{14}C-HC 20-511 (1 mg/kg, single dose). Milk and blood samples were collected 0.5, 1, 2, 4, 6, 8 and 24 hr after dosing. Radioactivity was calculated by a The results indicated that HC 20-511 was transferred to milk soon after dosing, and the radioactivity concentrations in milk were higher than in plasma.

***Toxicology*:**

Acute toxicity studies

Studies reviewed:

1. HC 20-511: An intravenous and oral acute toxicity study in mice, rats and rabbits. Vol. 1
2. HC 20-511: Pamoate versus hydrogen fumarate: A comparative acute intravenous toxicity study in mice. Vol. 1
3. HC 20-511 acute toxicity in rats during postnatal development. Vol. 1
4. Acute oral and intragastric toxicity studies of 20-511 in male and female rats 1, 7, 10, 14, 21 days and 5 weeks of age (Project T-1421, 1422, 1423, 1424, 1425, and 1427). Vol. 1
5. HC 20-511 (+) and (-) antipodes an acute oral toxicity study in mice. Vol. 1
6. Acute oral toxicity studies of Syrup in rats (T-1348, T-1349, T-1350, T-1351, T-1398, T-1427). Vol. 1
7. Acute oral LD_{50} toxicity study of Syrup (new formulation) in the rat (Project T-1763). Vol. 1
8. Acute toxicity-oral-theophyllin/ketotifen 300/1 in Sprague-Dawley rats-orientating study. Vol. 1
9. Acute oral toxicity studies in white mice (HC 20-511) by products (12-986, 21-829, T00031 CH). Vol. 1
10. An acute oral toxicity study with byproduct 509-83 (T00443) in mice. Vol. 1

Review:

[Reviewer's comment: In several acute toxicity studies, no vehicle control information was provided.]

1. HC 20-511: An intravenous and oral acute toxicity study in mice, rats and rabbits. Vol. 1

Report N^{o}: Not indicated
Compound: HC 20-511
Route: Oral or intravenous
Dosing Regimen: Single dose
Study Design:

Species	Dose (mg/kg)		N
	iv	po	(sex/group)
MF2 albino mice, 19-31 g	10, 13, 18	100, 180, 320, 560, 1000	5
OFA albino rats, 155-240 g	3.2, 4.2, 5.6, 7.5, 10	100, 180, 320, 560, 1000, 1800	5
Rabbits, 2.11-3.09 kg	10, 20, 40	320, 560, 1000, 1800	3-5

Study Site:

Report Time: December 14, 1971
GLP/QAU: No

The purpose of this study was to compare the acute toxicity of HC 20-511 following a single oral or intravenous administration in mice, rats and rabbits. The animals were observed over 7 days for mortality and clinical signs.

Results:

Mortality and clinical signs are summarized in the table below. Most clinical signs disappeared within 24 hr except that in rabbits receiving 1000 mg/kg of HC 20-511 (po), and in rats at 320 mg/kg and 560 mg/kg (po), the signs were reversed in 48 hr. The clinical signs in all species were similar and dose-dependent.

Mortality and clinical signs observed in mice, rats and rabbits

Dose (mg/kg, iv)	Mouse		Rat		Rabbit	
	Death	Sign	Death	Sign	Death	Sign
3.2			0/10	F, E, D 10/10 (< 22 hr)		
4.2			2/10	F, E, D 10/10 (< 22 hr)		
5.6			3/10	H, F, A, D 10/10, E 7/10 (< 18 hr)		
7.5			10/10	B, F, I, A, D 10/10		
10	0/10	F, E, G 10/10 (< 5.5 hr)	10/10	B, F, E, D 10/10	0/6	B, P, O, L, A, D, M, 6/6 (< 6 hr)

Dose (mg/kg, iv)	Mouse		Rat		Rabbit	
	Death	Sign	Death	Sign	Death	Sign
13	3/10	F, B, D 10/10, A, E, C 7/10 (< 20 hr)				
18	10/10					
20					2/6	B, H, F, I, L, A, D, M, 6/6 (< 24 hr)
40					6/6	B, J, H, F, K, L, N 6/6
Max. tolerated dose (mg/kg)	10		3.2		10	
LD_{50} (mg/kg)	13.8 ± 0.92		5.3 ± 0.36		21.0 ± 5.2	
Dose (mg/kg, po)	Death	Sign	Death	Sign	Death	Sign
100	0/10	E, D, C 10/10 (< 7 hr)	0/10	I, E, D 10/10, (< 24 hr)		
180	0/10	I, E, G, C 10/10 (< 24 hr)	2/10	H, E, D 10/10, (< 24 hr)		
320	5/10	B, A, D 10/10, I, E, C 5/10 (< 24 hr)	7/10	B, E, D 10/10, H 4/10, I 3/10 (< 24 hr)	0/6	A, D 10/10
560	9/10	B, A, D 10/10, I, E, C 1/10 (< 24 hr)	8/10	B, E, D 10/10, Q, I 3/10, R 5/10 (< 48 hr)	2/6	A, D 6/6, B, I 2/6 (< 24 hr)
1000	10/10	B, A, D 10/10	8/10	B, E, D 10/10, Q, I, A, G 2/10 (< 48 hr)	3/6	H, R, A, D 6/6 (< 48 hr)
1800			10/10	B, I, E, D 10/10	6/6	B, S, O, L, D 5/6, M 3/6, F 2/6, H 1/6
	Drowsiness (A), cramps (B), piloerection (C), forced and accelerated breathing (D), flaccidity (E), motor excitation (F), slowed respiration (G), jerking (H), prone position (I), muscular fibrillation (J), opisthotonus (K), lateral decubitus (L), blinking (M), gasping (N), running motions (O), tremor (P), hyperreflexia (Q), equilibrium disturbed ®, trismus (S)					
Max. tolerated dose (mg/kg)	100		100		320	
LD_{50} (mg/kg)	365 ± 53		360 ± 65		790 ± 145	

2. HC 20-511: Pamoate versus hydrogen fumarate: A comparative acute intravenous toxicity study in mice. Vol. 1

Report Nº: Not indicated
Compound: HC 20-511
HC 20-511
Route: Intravenous at a volume of 25 ml/kg
Dosing Regimen: Single dose
Dose Level: 30, 27, 24 and 13 mg/kg for pamoate; 24, 18, 13 and 10 for fumarate
Animal: Kfm:NMRI mice, 6 weeks old, 22-33 g, 2/sex/group
Study Site:
Study Duration: January 17 to February 2, 1989
Report Time: February 16, 1990
GLP/QAU: Yes

The purpose of this study was to compare the toxicity of two salts of HC 20-511. The animals were observed for 7 days following the treatment. Toxicity was assessed as shown below.

Toxicity assessment

Parameter	Procedure
Clinical signs and mortality	Daily
Body weights	Daily (5 days/week)
Gross pathology	At the end of the treatment, necropsy was performed on all animals. Animals that died during the observation were necropsied as soon as possible.
Organ weights	The following organs from each animal were weighed: adrenal, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid.
Histopathologic examinations	The following organs from all surviving animals were examined histopathologically: adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pancreas, spleen, testis, thymus, uterus and vagina.

Results:

A. Mortality and clinical signs: The data for mortality and clinical signs are presented in the following table. All deaths occurred within 6 hr after dosing. The maximum non-lethal doses for pamoate and fumarate were 13.0 and 10.0 approximately. The clinical signs were reversed within 24 hr.

Mortalities and clinical signs observed in study

	Ketotifen pamoate				Ketotifen fumarate			
Dose (mg/kg)	13	24	27	30	10	13	18	24
Mortality	0	1♀	1♂, 1♀	2♂, 2♀	0	1♂	1♀	2♂, 2♀
Drowsiness	0	0	2/4	4/4	0	1/4	1/4	4/4
Flaccidity	0	4/4	2/4	0	0	4/4	4/4	0
Convulsion, tonic	0	0	2/4	4/4	0	1/4	1/4	4/4
Prone position	0	0	2/4	4/4				
Forced breathing	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4

B. Body weights: No significant body weight loss was noted.

C. Gross and histopathology examinations: No treatment-related findings were observed. [**Reviewer's Comment**: No detailed data were presented.]

Conclusion: The toxicity profiles of HC 20-511 fumarate and pamoate were similar. The NOAEL for ketotifen fumarate was less than 10 mg/kg in this study.

3. HC 20-511 acute toxicity in rats during postnatal development. Vol. 1 [redacted]

Report Nº: Not indicated
Compound: HC 20-511 [redacted]
Route: Intragastric (1-day group only) or oral
Dosing Regimen: Single dose
Dose Level: 10, 20, (Intragastric only) 40, 80, 160, 300, 450 and 600 mg/kg

Animal: Albino OFA rats (SPF), 1 (7.3-7.7 g), 10 (24.1 g), 21 (50.1 g) and 30 (103 g) days old, 10/sex/group

Study Site:

Report Time: January 4, 1977

GLP/QAU: No

The purpose of this study was to compare the acute toxicity of HC 20-511 in pups of rats at an age of 1, 10, 21 and 30 days post partum (pp). The animals were observed for 14 days following a single oral administration. Mortality, clinical signs and body weight gain were observed. [**Reviewer's comment**: No detailed observation procedures were provided.]

Results:

A. Mortality: The following table summaries the values of LD in different treatment groups

Values of LD in different treatment groups (mg/kg)

Group	Males			Females		
	LD_5	LD_{50}	LD_{95}	LD_5	LD_{50}	LD_{95}
1 day	12.2	602.1	29617.1	94.2	596.2	3775.1
10 days	66.6	160.6	387.6	98.9	191.3	370.0
21 days	171.4	486.4	1380.4	141.7	344.3	836.3
30 days	272.9	710.1	1847.9	144.2	416.9	1204.9
10 weeks		360			360	

B. Clinical signs: Clinical signs are summarized in the table below.

Clinical signs in rats treated with HC 20-511

Signs	1 day	10 days	21 days	30 days
Sedation		+	+	+
Motor excitation		+	+	+
Ataxia		+	+	+
Spastic paralysis			+	+
Tremor		+	+	+
Hyperreflexia		+	+	+
Prone position			+	+
Pale skin	+	+	+	+
Piloerection			+	+
Accelerated breathing	+	+	+	+
Forced breathing	+	+	+	+
Spastic breathing	+	+	+	+
Cyanosis	+			
Well tolerat. dose	40 mg/kg	40 mg/kg	80 mg/kg	80 mg/kg
	Clinical signs started from 80 mg/kg, and resolved in 3 hr in surviving animals.	Clinical signs started from 80 mg/kg, and resolved in 3 hr in surviving animals.	Clinical signs started from 160 mg/kg, and resolved in 6 hr in surviving animals.	Clinical signs started from 160 mg/kg, and resolved in 6 hr in surviving animals.

C. Body weights: Body weight changes are summarized in the table below. Animals treated with high doses of ketotifen showed a decrease in body weight gain.

Body weight gains in rats 14 days after the treatment with a single dose of HC 20-511

Dose (mg/kg)	Control	10	20	40	80	160	300	450	600
1 day									
Gain (g)	34.2	34.7	32.4	32.9	34.6	32.7	31.0	31.7	29.8
% control	100	101.5	94.7	96.2	101.2	95.6	90.6	92.7	87.1
10 days									
Gain (g)	71.9			69.4	67.8	67.1	62.2		
% control	100			96.5	94.3	93.3	86.5		
21 days, ♂									
Gain (g)	137				134	126	134	133	135
% control	100				97.8	92.0	97.8	97.1	98.5
21 days, ♀									
Gain (g)	121				120	118	121	120	114
% control	100				99.2	97.5	100	99.2	94.2
30 days, ♂									
Gain (g)	200				204	191	198	199	199
% control	100				102	95.5	99	99.5	99.5
30 days, ♀									
Gain (g)	157				159	151	153	147	142
% control	100				101.2	96.2	97.5	93.6	90.4

D. Necropsy: In 1-day and 10-day animals treated with higher doses, a dark-brown discoloration of the gastrointestinal tract was seen, which was reversed to normal within the following 72 hr. No other unusual findings were observed.

Conclusion: Based on LD_{50} and other toxicity data, the suckling animals (10 days old) were more sensitive to the acute lethal effects of HC 20-511 compared to newborn, weanling and young rats.

4. **Acute oral and intragastric toxicity studies of 20-511 in male and female rats 1, 7, 10, 14, 21 days and 5 weeks of age (Project T-1421, 1422, 1423, 1424, 1425, and 1427). Vol. 1**

This study was reviewed by Dr. Dou Huey Jean on October 8, 1980. Reference Review and Evaluation of Pharmacology and Toxicology Data dated October 8, 1980 (Attachment 5).

5. **HC 20-511 (+) and (-) antipodes an acute oral toxicity study in mice. Vol. 1**

Report Nº: Not indicated
Compound: HC 20-511

Route: Oral
Dosing Regimen: Single dose
Dose Level:
Mixture: 275-730 mg/kg
Animal: OF1 mice, 10/sex/group
Study Site:
Report Time: February 19, 1990
GLP/QAU: No

The purpose of this study was to compare the acute toxicity of (+) and (-) antipodes of HC 20-511 following a single oral administration. The animals were observed over 14 days for mortality and clinical signs. A post mortem examination was carried out on all animals.

Results:

LD values are summarized in the table below. Clinical signs observed included drowsiness, cramps, jumping, prone position, piloerection, motoric unrest, and dyspnea [**Reviewer's comment**: No detailed information was provided.]. No differences were noted between the 2 drug groups. No visible damage was noted in macroscopic examination.

LD values (mg/kg, po)

	(+) HC 20-511	(-) HC 20-511	1:1 Mixture	HC 20-511
LD_5	210	416	255	199
LD_{50}	371	749	390	342
LD_{95}	654	1349	595	587

6. Acute oral toxicity studies of : Syrup in rats (T-1348, T-1349, T-1350, T-1351, T-1398, and T-1427). Vol. 1

Report N°: T-1-1/25/80
Compound: HC 20-511
Route: Oral
Dosing Regimen: Single dose
Animal: Sprague-Dawley rats, 5-week old
Study Site:
Report Time: January 29, 1980
GLP/QAU: Yes

Study Design:

	Acute oral toxicity studies of 20-511			Acute oral toxicity studies of		
Project #	T-1348	T-1398	T-1427	T-1349	T-1350	T-1351
N	10♂/dose	10♂/dose	5/sex/dose	2♂/dose	10♂/dose	10♂/dose
Wt. (g)	84-141	91-151	98-118♂,91-100♀	90-116	90-125	91-138
Formulation						
Dose (mg/kg)	101-1066	78-373	78-287	10-50 ml/kg	20-45 ml/kg	20-48 ml/kg

The purpose of this study was to determine the acute toxicity of HC 20-511 in Syrup formulation. The animals were observed for 7 days following a single oral administration. Mortality and clinical signs were observed. [**Reviewer's comment**: No detailed observation procedures were provided.]

Results:

A. Mortality: The following table summaries the values of LD_{50} in different treatment groups

Values of LD_{50} in different treatment groups (mg/kg)

	Acute oral toxicity studies of 20-511			Acute oral toxicity studies of		
Project #	T-1348	T-1398	T-1427	T-1349	T-1350	T-1351
N	10♂/dose	10♂/dose	5/sex/dose	2♂/dose	10♂/dose	10♂/dose
Formulation						
LD_{50} (mg/kg)	125	156	161	7 (35 ml/kg)	6 (31.1 ml/kg)	41.4 ml/kg
Maximum nonlethal dose (mg/kg)		78	101 (♂) 78 (♀)	6 (30 ml/kg) 100% mortality at 8	4.8 (24 ml/kg)	24 ml/kg

B. Clinical signs: The clinical signs observed in groups T-1348, T-1398 and T-1427 included decreased locomotor activity, ataxia, hypothermia, weak and loss of righting reflex. In the animals treated with Syrup formulation (including control), the clinical signs were decreased locomotor activity, ataxia, ptosis. In T-1350 animals, sedation, hypothermia and cyanosis were noted at high doses (35-45 ml/kg), while in T-1351 animals at the doses higher than 34 ml/kg, moderate clonic convulsions and muscle tremor were observed. The surviving animals appeared normal 24 hr after dosing.

7. Acute oral LD_{50} toxicity study of [redacted] Syrup (new formulation) in the rat (Sandoz Project T-1763). Vol. 1

Report N^{o}: T-1-10/27/82
Compound: [redacted]
Route: Oral
Dose Level: 10, 18, 26, 34, 42 or 50 ml/kg
Dosing Regimen: Single dose
Animal: Charles River CD rats, 5-8-day old, and 150-day old
Study Site: [redacted]
Experimental period: June 17, 1982 to August 2, 1982
Report Time: October 27, 1982
GLP/QAU: Yes
Study Design:

							Syrup vehicle control					
Dose (ml/kg)	10	18	26	34	42	50	10	18	26	34	42	50
Dose (mg/kg)	1	1.8	2.6	3.4	4.2	5.0	1	1.8	2.6	3.4	4.2	5.0
(#/sex/dose)												
Pup	5	5	5	5	5	5	5	5	5	5	5	5
Adult	5	5	5	5	5	5	5	5	5	5	5	5

The purpose of this study was to compare the acute toxicity of [redacted] between 5-8-day old rats and 150-day old rats. The animals were observed for 14 days following a single oral administration. The day of dosing was designated as Day 1. Mortality and clinical signs were observed daily. Body weights were measured on Days 1, 8 and 15.

Results:

A. Mortality: The following table summaries the deaths noted in this study.

Mortality data of the rats treated with [redacted] or vehicle

							Syrup vehicle control					
Dose (ml/kg)	10	18	26	34	42	50	10	18	26	34	42	50
Dose (mg/kg)	1	1.8	2.6	3.4	4.2	5.0	1	1.8	2.6	3.4	4.2	5.0
N	10	10	10	10	10	10	10	10	10	10	10	10
Pup	0	0	3	10	10	6	1	1	3	9	6	10
LD_{50}	29.7 ml/kg (2.97 mg/kg)						27.3 ml/kg					
Adult	0	0	5	10	10	10	0	1	5	10	10	10
LD_{50}	25.3 ml/kg (2.53 mg/kg)						24.5 ml/kg					

B. Clinical signs: The clinical signs observed in 150-day old rats are listed in the table below. No differences between the control and ketotifen-treated animals were noted. **[Reviewer's comment**: No clinical observation data for 5-8-day old rats were provided.]

Incidence of clinical signs with the 150-day old rats

	Syrup vehicle control											
Dose (ml/kg)	10	18	26	34	42	50	10	18	26	34	42	50
Dose (mg/kg)	1	1.8	2.6	3.4	4.2	5.0	1	1.8	2.6	3.4	4.2	5.0
N	10	10	10	10	10	10	10	10	10	10	10	10
↓ locomotor activity	9	10	10	9	9	9	10	10	10	10	10	10
Ataxia		6	8	8	8	4		9	10	5	6	1
Loss righting reflex		3	4	5	9	4		4	5	6	4	1
Salivation			1	6	5	8			2	5	6	8
Hypothermia		1	3	2					2			
Ptosis			1	5	5	8		2	1	7	5	7
Mucoid diarrhea		9	10	9	9	9	4	10	10	8	9	10

C. Body weight changes: No differences between the control and ketotifen-treated rats, and between low and high doses groups were noted following 14-day observation.

In conclusion, pups and adult rats were treated with a single oral dose of [redacted] Syrup or vehicle and observed for 14 days. No differences regarding mortality, clinical signs (adult rats only) and body weight changes between the pups and the adult rats, and between the animals treated with low doses and high doses, were noted. The results in this study, including the low LD_{50}, supported that the mortalities and clinical observations were induced by vehicle.

8. Acute toxicity-oral-theophyllin/ketotifen 300/1 in Sprague-Dawley rats-orientating study. Vol. [redacted]

Report Nº: Not indicated
Compound: [redacted]
Route: Oral by stomach tube
Dose Level: 100, 215, 316, 464, 681, 1000 and 1470 mg/kg
Dosing Regimen: Single dose
Animal: Sprague-Dawley rats, 40-50 days old, 156-180 g
Study Site: [redacted]
Experimental period: October 1 to 14, 1985
Report Time: October 15, 1985
GLP/QAU: Yes

The purpose of this study was to determine the acute toxicity of KT 1/300 following a single oral administration to rats. The animals were observed for 14 days following a single oral administration. Mortality, clinical signs, body weight and food

consumption were observed. All surviving and dead animals were inspected macroscopically. [**Reviewer's comment**: No detailed observation procedures were provided.]

Results:

A. Mortality: The following table summaries the mortalities and clinical signs observed in different treatment groups. Deaths occurred between 15 min and 24 hr following dosing. The LD_{50} was 690 mg/kg in males, and 580 mg/kg in females. All surviving animals were free of symptoms within 8 to 24 hr.

Clinical observations and deaths in rats treated with KT 1/300

Dose (mg/kg)	100	215	316	464	681	1000	1470
N	3♂, 3♀	3♂, 3♀	3♂, 3♀	3♂, 3♀	3♂, 3♀	3♂, 3♀	3♂
Muscular hypotonia		6/6	6/6	6/6	6/6	6/6	3/3
Mydriasis		6/6	6/6	6/6	6/6	6/6	3/3
Bradyponea		2♀					
Reduced motility			6/6	6/6	6/6	6/6	3/3
Ataxia			1♂, 3♀	6/6	6/6	6/6	3/3
Dyspnea			6/6	6/6	6/6		3/3
Ptosis			6/6	1♂, 3♀	6/6	6/6	3/3
Tremor				1♀			
Clonic convulsions				1♀	2♂, 2♀	2♂, 3♀	3/3
Death				1♂, 1♀	2♂, 2♀	2♂, 3♀	3/3

B. Body weight gain and food consumption: No inhibition of body weight gain and food consumption was observed.

C. Gross necropsy and histopathological examinations: Gross necropsy performed on the dead animals showed that the livers in these rats were slightly cloudy and partially fine grained structured. Histological examination showed no pathological findings. In the surviving animals, no treatment-related abnormal findings were noted.

Conclusion: Rats were treated with a single oral dose of KT 1/300 and observed for 14 days. Mortalities occurred at the doses higher than 464 mg/kg. Clinical signs included reduced motility, ataxia, dyspnea and muscular hypotonia, which, in surviving rats, were reversed within 24 hr. The NOAEL was determined as 215 mg/kg.

9. Acute oral toxicity studies in white mice: [redacted] (HC 20-511) by products (12-986, 21-829, T00031 CH). Vol. 1

Report Nº: Not indicated
Compound: [redacted]

Route: Oral
Dosing Regimen: Single dose
Dose Level: Not indicated

Animal: albino mice, 16-29 g, 10/sex/group
Study Site:

Report Time: March 26, 1978
GLP/QAU: No

The purpose of this study was to compare the acute toxicity of ketotifen fumarate and its synthesis byproducts following oral administration. The animals were observed over 14 days for mortality, body weights and clinical signs. A post mortem examination was carried out on all animals.

Results:

LD values are summarized in the table below. The following clinical signs observed 5-15 min after dosing in all animal groups were similar: drowsiness, convulsions and twitching, piloerection, recumbence, and dyspnea. Up to 30% of body weight loss was noted, which returned to normal "subsequently". No gross examination data were provided.

LD values for different compounds (mg/kg, po)

	12-986	21-829	T00031 CH	HC 20-511
LD_5	209	2000	774	199
LD_{50}	293	3222	1209	342
LD_{95}	411	5191	1889	587

10. An acute oral toxicity study with byproduct 509-83 (T00443) in mice. Vol. 1

Mice (Kfm-NMRI) were treated with the byproduct, 509-83 at a single oral dose of 300-1000 mg/kg and observed for 14 days. The LD values were LD_5, 632 mg/kg; LD_{50}, 879 mg/kg; LD_{95}, 1221 mg/kg. Since the LD_{50} was higher than that of HC 20-511 (342 mg/kg), the sponsor concluded that this byproduct did not affect HC 20-511's toxicological profile.

Subchronic studies

Studies reviewed:

1. Three weeks toxicity studies of 20-511 in rats [dietary administration (Project T-1100), gavage administration (Project T-1101)]. Vol. 2
2. HC 20-511: Toxicity study of rats treated orally for 5 weeks. Vol. 2
3. HC 20-511 Electron microscope analysis of rat liver and kidney after chronic treatment. Vol. 2
4. HC 20-511: A 13-week oral toxicity study in rats. Vol. 2
5. HC 20-511: Biochemical changes in the livers of rats treated for 13 weeks. Vol. 2

6. Recovery study in rats after 13-week oral treatment. Vol. 2
7. HC 20-511: Ultrastructural findings in rat livers after treatment for 13 weeks. Vol. 2
8. HC 20-511: A 13-week oral toxicity study in dogs. Vol. 3
9. HC 20-511: A 13-week oral toxicity study in dogs—additional low dose. Vol. 3
10. 13-week toxicity of ketotifen/theophylline 1/300, Lot # 231-called for short "KT 1/300"-by oral administration to beagle dogs. Vol. 10, Page 257.

Review:

1. **Three weeks toxicity studies of 20-511 in rats [dietary administration (Project T-1100), gavage administration (Project T-1101)]. Vol. 2**

Report Nº: T-1-8/24/80
Compound: 20-511
Route: Dietary mixture (T-1100) or gavage (T-1101)
Dose Level: T-1100: 1, 9 and 83 mg/kg; T-1101: 1, 10 and 100 mg/kg
Dosing Regimen: Daily x 26 to 27 days
Animal: rats, 5-week old, 140-241 g (T-1100) and 145-267 g (T-1101)
Study Site:
Report Time: August 23, 1978
GLP/QAU: No
Study Design:

Group	Dose (planned)	Dose (actual)	N	Dose
T-1100	(mg/kg)	(mg/kg)	(sex/group)	Concentration (%)
1	Control	Control	8	
2	1	1	8	0.001
3	10	9	8	0.01
Group	Dose (planned)	Dose (actual)	N	Dose
T-1100	(mg/kg)	(mg/kg)	(sex/group)	Concentration (%)
4	100	83	8	0.1
T-1101				
1	Control	Control	8	
2	1	1	8	0.1
3	10	10	8	0.1
4	100	100	8	1

The purpose of this study was to compare the toxicity of 20-511 in rats by dietary and gavage administrations for 3 weeks. The day of the first dosing was designated as Day 1. Toxicity was assessed as shown below.

Toxicity assessment

Parameter	Procedure
Clinical observations	Daily

Parameter	Procedure
Body weights	Weekly
Food consumption	Weekly
Clinical pathology	On Days 19 or 20, and at sacrifice, Groups 1, 3 and 4, 5/sex/group
Urinalysis	Day 11 or Day 12, Groups 1, 3 and 4, 5/sex/group
Ophthalmoscopic examinations	Day 19
Gross pathology	On Days 27 and 28, all animals were euthanized. A complete gross pathology examination was conducted on all animals.
Organ weights	The following organs from each animal were weighed: adrenal, brain, heart, liver, lungs, uterus, pituitary, spleen, gonads, thymus, thyroid and perirenal fat.
Histopathologic examinations	The following organs from 5 animals/sex in the control and high dose groups were examined histopathologically: adrenal gland, aorta, bone, brain, cervix, epididymis, eye and lens, gross lesions, heart, liver, lung, lymph node, mammary gland, nerve, ovary, pancreas, perirenal fat, pituitary gland, prostate gland, salivary gland, seminal vesicle, skeletal muscle, small and large intestine, skin, spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, oviduct, uterus. The following tissues were selected from all animals for histopathological examination: liver, kidney, thyroid and all gross lesions.

Results:

A. Clinical observations: No mortality and treatment-related findings were noted.

B. Body weights: Body weight changes are summarized in the table below. A decrease in body weight gain at high dose was noted.

Body weight changes in rats treated with ketotifen (g)

Group	Dose	Week 0 (Day 1)		Week 3		% of control		Body wt. gain		% of control	
T-1100	(mg/kg)	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	Control	225.9	167.0	306.7	207.0	100	100	80.8	40	100	100
2	1	224.0	165.7	308.1	207.9	100	100	84.1	42.2	104.1	105.5
3	10	222.5	156.0	308.0	194.1	100	94	85.5	38.1	105.8	95.3
4	100	219.0	159.1	286.7	195.1	93	94	67.7	36	83.8	90
T-1101											
1	Control	221	165	309	210	100	100	88	45	100	100
2	1	219	169	313	216	100	100	94	47	106.8	104.4
3	10	216	164	314	200	100	95.2	98	36	111.4	80
4	100	219	162	296	200	96	95.2	77	38	87.5	84.4

C. Food consumption: No toxicologically significant changes were observed.

D. Clinical pathology: No toxicologically significant changes were observed.

E. Ophthalmoscopy: No treatment-related changes were noted.

F. Urinalysis: No treatment-related differences were noted.

G. Total liver lipids: The liver lipid levels were increased in high dose male animals (see table below).

Total liver lipids in rats treated with 20-511 for 3 weeks

	T-1100				T-1101			
Group ♂	Control	Low	Mid	High	Control	Low	Mid	High
Lipid (mg/g)	54.5±2.9	53.5±3.8	56.4±1.7	64.8±4.1	53.2±0.3	50.2±5.3	53.0±3.1	70.9±6.4
Group ♀	Control	Low	Mid	High	Control	Low	Mid	High
Lipid (mg/g)	54.9±4.2	59.7±2.5	55.0±3.5	57.9±6.5	54.9±3.7	52.2±2.1	57.0±4.3	56.1±5.7

H. Organ weights: Liver weights were increased in high dose animals and low dose female animals (see table below). No other toxicologically significant changes were noted.

Liver and thyroid weight changes in rats treated with 20-511 for 3 weeks

	T-1100				T-1101			
Group ♂	Control	Low	Mid	High	Control	Low	Mid	High
Liver (g)	10.06±1.0	10.2±0.9	10.3±0.9	11.2±0.9	10.5±0.9	10.5±0.7	10.2±1.0	12.2±0.5
Relative (%)	3.37±0.2	3.44±0.2	3.46±0.3	4.11±0.3	3.52±0.2	3.5±0.1	3.4±0.2	4.3±0.2
Group ♀	Control	Low	Mid	High	Control	Low	Mid	High
Liver (g)	6.51±0.8	6.38±0.5	6.0±0.7	6.5±0.6	6.31±0.5	7.0±0.6	5.8±0.8	7.4±0.7
Relative (%)	3.30±0.36	3.30±0.1	3.38±0.2	3.61±0.1	3.22±0.1	3.5±0.2	3.2±0.2	4.1±0.4

I. Gross and histopathological examinations: No toxicologically significant changes were noted in necropsy. In microscopic examinations, periportal lipidosis was noted in all groups, but high dose animals showed a higher degree of lipidosis (see table below).

Liver periportal lipidosis in rats treated with 20-511 for 3 weeks

	T-1100				T-1101			
Group ♂	Control	Low	Mid	High	Control	Low	Mid	High
Trace	7/8	5/8	5/8	1/8	7/8	4/8	8/8	3/8
Minimal	1/8	3/8	3/8	5/8	1/8	4/8		1/8
Mild				1/8				3/8
Moderate				1/8				
♀								
Trace	4/8		3/8	4/8	3/8	2/8	3/8	1/8
Minimal	2/8	4/8	3/8	2/8	5/8	3/8	4/8	5/8
Mild	1/8	3/8	2/8	2/8		3/8	1/8	2/8
Moderate		1/8						

In conclusion: No differences in toxicity of the drug between these two administration groups were noted. Rats were treated with ketotifen fumarate (po) for 3 weeks. Decreased body weight gain was noted in animals at high dose. In male rats at high dose, an increase in total liver lipids was observed. Both male and female rats receiving high dose of ketotifen showed liver weight increase and a slightly higher degree of liver lipidosis relative to control animals. The NOAEL was 10 mg/kg in this study.

2. HC 20-511: Toxicity study of rats treated orally for 5 weeks. Vol. 2

Report N°: 257R
Compound: HC 20-511

Route: Oral
Dose Level: 0, 1, 10 and 25 mg/kg
Dosing Regimen: qd x 5 weeks
Animal: [redacted] SPF rats, 8-week old, 215-217 g for males and 160-180 g for females, 7/sex/group
Study Site: [redacted]
Study Period: July 7 to September 1, 1980
Report Time: September 30, 1980
GLP/QAU: Yes

The purpose of this study was to determine the cardiovascular effects of 20-511 in rats. The rats were treated with HC 20-511 for 5 weeks followed by a 3-week recovery period. Toxicity was assessed as shown below.

Toxicity assessment

Parameter	Procedure
Clinical observations	Daily
Body weights	Weekly
Food consumption	Weekly
ECG	Before and 5 weeks after the initiation of treatment, and at Weeks 1 and 2 during the recovery period.

Results:

A. Clinical observations: No mortality and treatment-related findings were noted.

B. Body weights: Body weight changes are summarized in the table below. A decrease in body weight gain in female rats at high dose was noted, which showed recovery tendency during the recovery period.

Body weight changes in rats treated with ketotifen for 5 weeks (g)

Group	Dose	After 5 weeks		Body weight gain		% of BW gain		Recovery BW gain	
	(mg/kg)	♂	♀	♂	♀	♂	♀	♀	
1	Control	312±30	198±8	27.9±7	10.2±1.7	100	100	7.5	100
2	1	299±16	201±6	25.5±3.6	10.2±1.4	91.4	100	7.4	98.7
3	10	307±9	193±8	25.8±2.6	8.2±2.0	92.5	80.4	6.5	86.7
4	25	302±18	187±8	26.3±2.8	7.0±2.0	94.3	68.6	5.8	77.3

C. Food consumption: No toxicologically significant changes were observed.

D. ECG: No treatment-related differences in ECG were observed.

In conclusion, rats were treated with HC 20-511 at 1, 10 and 25 mg/kg/day for 5 weeks followed by a 3-week recovery period. The drug was well tolerated. Female rats at mid and high dose showed a decrease in body weight gain, which was partially recovered 3 weeks after stopping drug administration. No treatment-related ECG changes were noted.

3. HC 20-511 [redacted] Electron microscope analysis of rat liver and kidney after chronic treatment. Vol. 2 [redacted]

Report N^{o}: Not indicated
Compound: HC 20-511 [redacted]
Route: Oral
Dose Level: 0, 4, 10, 25, 60 and 150 mg/kg/day
Dosing Regimen: qd x 5 weeks
Animal: [redacted] rats, 6-week old
Study Site: [redacted]

Report Time: March 28, 1980
GLP/QAU: No

The purpose of this study was to determine the liver and kidney toxicity of 20-511 in rats. The rats were treated with HC 20-511 for 5 weeks (4/sex/group) followed by a 5-week recovery period (2/sex/group). The livers and kidneys from 2 rats/sex/dose were prepared for ultrastructural examination after 5-week treatment. Specimens from 2 other rats/sex/dose were prepared after the recovery period.

Results:

A. Liver: Treatment-related changes in livers were listed in the table below.

Liver changes in rats treated with HC 20-511 for 5 weeks

Treatment	Control, 4 and 10 mg/kg	25 mg/kg	60 mg/kg	150 mg/kg
Lipid droplet	Quantitavely increased	Increased more	Obviously increased	♀: Markedly increased.
Glycogen	Decreased			
Mitochondrial content	Increased			
SER*	Evident in some hepatocytes	More prominent	More prominent	Proliferation
Myeloid body	Occasionally seen in the interhepatic space		Transformation of lipid droplet to myeloid body was obvious.	♂: Increased formation, and decreased exocytotic function.
Bile canaliculi			Enlarged	
Recovery			↓# of lipid droplets. Myeloid bodies: disappeared. SER: visible in small areas. Glycogen: reappeared.	

*SER Smooth endoplasmic reticulum

B. Kidney: Treatment-related changes in kidneys were listed in the table below.

Kidney changes in rats treated with HC 20-511 for 5 weeks

Treatment	Control and 4 mg/kg	10 and 25 mg/kg	60 and 150 mg/kg
Lipid droplet		Slight increase	Obvious. Myeloid bodies were rare.

Treatment	Control and 4 mg/kg	10 and 25 mg/kg	60 and 150 mg/kg
Thickening of the basement membrane	Yes	Yes	Yes
Recovery		No lipid droplet	↓fat inclusion but still obvious.

In conclusion: Increased lipid induction in liver and kidney tubular epithelial cells was seen at high and maximal doses. An increase in SER and a decrease in glycogen were also noticed in liver. After recovery period, the phospholipidosis in males at maximal dose was reversible, while the increased lipid droplet content, although reduced, remained evident. Four mg/kg/day was determined as NOEL in this study.

4. **HC 20-511: A 13-week oral toxicity study in rats. Vol. 2**

This study was reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Reference Pharmacology Review Original Summary submitted 3/9/77 (Attachment 1), Page 6.

5. **HC 20-511: Biochemical changes in the livers of rats treated for 13 weeks. Vol. 2**
6. **Recovery study in rats after 13-week oral treatment. Vol. 2**
7. **HC 20-511: Ultrastructural findings in rat livers after treatment for 13 weeks. Vol. 2**

These studies were reviewed by Dr. Gamil Debbas (HFD-160) on September 5, 1978 and November 30, 1978. Reference Pharmacology Review Amendment dated June 8, 1978 (Attachment 2), Page 5 and 3, and Amendment dated September 20 (Attachment 3), 1978, Page 10.

8. **HC 20-511: A 13-week oral toxicity study in dogs. Vol. 3**
9. **HC 20-511: A 13-week oral toxicity study in dogs—additional low dose. Vol. 3**

These studies were reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Reference Pharmacology Review Original Summary submitted 3/9/77 (Attachment 1), Page 11.

10. **13-week toxicity of called for short "KT 1/300"-by oral administration to beagle dogs. Vol. 10, Page 257.**

Report Nº: Not indicated
Compound:

Route: Oral

Dosing Regimen: 16-200 mg/kg/day by capsule, qd x 13 weeks
Animal: Beagle dogs, age 10-15 months, 7.9-10.3 kg for males, age 14-16 months, 6.9-8.8 kg for females
Study Site: [redacted]
Date of Study Initiation: October 29, 1985
GLP/QAU: Yes
Study Design:

Groups	Treatment	N/sex	N/sex
Beagle dogs	KT 1/300 mg/kg/day, qd x 13 weeks		(recovery)
1	Control	5	1
2	16	4	0
3	40	4	0
4	Days 1-63: 100; Days 64-66: 200; Days 67-91: 100	5	1

One dog/sex/group was selected for an interim dissection after 4 weeks. On Day 64, the dose in 100 mg/kg/day was increased to 200 mg/kg/day due to lack of toxicity. On Day 67, the dose was returned to 100 mg/kg/day due to mortality occurred in 1 dog.

The purpose of this study was to evaluate the tolerance of dogs to KT 1/300 following daily oral administration for 13 weeks. The day of the first dosing was designated as Day 1. Toxicity was assessed as shown below.

Toxicity assessment

Parameter	Procedure
Clinical observations	Daily
Body weights	Weekly
Food and water consumption	Daily
Clinical pathology	Blood samples were collected from all animals prior to the first treatment, in Weeks 4 and 13, and in Week 17 for recovery dogs for hematology and clinical chemical examinations.
Urinalysis	Urine samples were collected from all animals prior to the first treatment, in Weeks 3 and 12, and in Week 16 for recovery dogs.
ECG	On Day 1, Weeks 4 and 13 in all dogs, and Week 17 on recovery dogs.
BP	In Weeks 4 and 13 in all dogs, and Week 17 in recovery dogs.
Ocular, hearing and dentition examinations	Ophthalmoscopic examination, auditory acuity examination and dentition inspection were performed in selected animals in Weeks 4 and 13, and in recovery dogs in Week 17.
Gross pathology	At the end of the treatment (Weeks 4, 13 or 17), animals were euthanized. A complete gross pathology examination was conducted.
Organ weights	The following organs from each animal were weighed: adrenal, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid.
Histopathologic examinations	The following organs from all animals were examined histopathologically: adrenal gland, aorta, bone (femur), bone marrow, brain, caecum, epididymis, esophagus, eyes, gall bladder, gross lesions, heart, kidney, large and small intestines, liver, lung, lymph node (mesenteric), mammary gland, ovary, pancreas, pituitary gland, prostate gland, salivary gland, seminal vesicle, skeletal muscle, peripheral nerve, skin, spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, uterus and vagina.

Results:

A. Clinical observations: One male animal at high dose group died on Day 66 (after treated with the drug at 200 mg/kg/day for 3 days). Comatous condition was seen for a short time before the death occurred. The cause of death was unknown. Vomiting (once or repeated, single to a few days a week) was noted in all treated groups, and slight sedation was noted in most high dose animals (see table below) for 22 hr on Day 66. There were no differences in clinical observations among different animal groups during the 4-week recovery period.

Clinical signs observed in animals

Dose	Male animals		Female animals	
(mg/kg/day)	Vomiting	Sedation	Vomiting	Sedation
Control	0/5	0/5	0/5	0/5
16	0/4	0/4	3/4 (2 weeks to 10 weeks)*	0/4
40	3/4 (1 week to 4 weeks)	0/4	0/4	0/4
100/200/100	4/5 (1 week to 4 weeks)	2/4 Day 66	4/5 (1 week to 10 weeks)	4/4 Day 66

*(): Number of weeks in which vomiting was observed.

B. Body weights: No treatment-related findings in body weights or body weight gain were noted during the treatment and recovery periods.

C. Food consumption: No drug-related differences in food consumption were observed.

D. Clinical pathology: No toxicologically significant findings were observed. Serum total bilirubin was increased in treated animal groups (see table below), which, without corresponding pathological changes, was not toxicologically meaningful.

Total serum bilirubin in dogs treated with [ ] (μmol/L serum)

Group	Dose	Males			Female		
	(mg/kg/day)	Start	Week 4	Week 13	Start	Week 4	Week 13
1	Control	3.32	2.68	2.44	3.28	3.42	3.33
2	16	3.03	3	2.87	3.2	3.53	3.57
3	40	3.25	3.18	3.33	3.03	4.18	3.67
4	100/200/100	3.04	3.8	4.13	2.98	4.6	4.6

E. Urinalysis: No treatment-related changes were noted.

F. ECG and blood pressure: In treated animals, an increase in heart rate was observed (see table below) at weeks 4 and 13. It seemed that the increased heart rate was reversible in males at mid dose and in females at high dose. No other treatment-related changes were noted. During recovery period, no differences were observed. The measurements of blood pressure showed no differences between control and treated animals.

Heart rate changes in animals treated with [redacted] (pulse/min)

Group	Dose	Week 1		Week 4		Week 13	
Males	(mg/kg/day)	Before dosing	2 hr after dosing	Before dosing	2 hr after dosing	Before dosing	2 hr after dosing
1	Control	118.4	105.2	127.8	111.8	106.8	103.3
2	16	124.5	125.3	129.3	130	131	122
3	40	96.8	104	121.8	131.3	118	109.3
4	100/200/100	123.8	111.2	137	138.6	151.7	132
Females							
1	Control	98.6	92.2	117.6	104	118	108.8
2	16	94.5	91.8	111.8	109.5	123.3	122
3	40	92.8	98.3	130.5	107.3	104.7	113
4	100/200/100	101	110	136.8	136	116	116

G. Ocular, hearing and dentition examinations: No treatment-related differences were observed.

H. Organ weights: No toxicologically significant changes were noted.

I. Gross and histopathology examinations: No treatment-related differences were noted in gross examinations.

In conclusion: Dogs were treated with [redacted] (16 to 200 mg/kg/day) by capsule for 13 weeks followed by a 4-week recovery period. One dog treated with the drug at 200 mg/kg/day died with unknown reason. Slight sedation was noted in animals at 200 mg/kg/day on Day 66. Increased heart rate and vomiting were found in all dose groups, which might be due to theophylline's pharmacologic effects. Exclusive of these pharmacologic effects, 100 mg/kg/day could be chosen as NOAEL.

Chronic toxicity studies:

Studies reviewed:

1. One year oral toxicity study in beagle dogs. Vol. 4 [redacted]
2. HC 20-511 one year oral toxicity study in dogs – additional low dose. Vol. 4 [redacted]
3. HC 20-511 supplementary 52 week oral toxicity study in beagle dogs. Vol. 5 [redacted]
4. HC 20-511: 52 weeks peroral toxicity study in rhesus monkeys. Vol. 5 [redacted]

Review:

1. **One year oral toxicity study in beagle dogs. Vol. 4** [redacted]
2. **HC 20-511 one year oral toxicity study in dogs – additional low dose. Vol. 4** [redacted]

These studies were reviewed by Dr. Gamil Debbas (HFD-160) on June 3, 1977. Refer to Pharmacology Review of [redacted] Original Summary submitted 3/9/77 (Attachment 1), Page 16.

In Study 1, the results of BSP test, which were not submitted when Dr. Debbas was reviewing the drug in 1977, were provided in this NDA submission. No abnormal findings were noted.

3. HC 20-511 supplementary 52 week oral toxicity study in beagle dogs. Vol. 5

[redacted]

Study Nº: 151 D2
Compound: HC 20-511 [redacted]
Route: Oral
Dose Level: 50 mg/kg/day x 52 weeks
Animal: Male beagle dogs, age 8-8.5 months, 5/group
Study Site: [redacted]
Report Time: January 30, 1978
GLP/QAU: No

The purpose of this study was to determine whether HC 20-511 was responsible for the formation of bladder concrements in beagle dogs treated with HC 20-511 at high dose (50 mg/kg/day) for 52 weeks. Toxicity was assessed as shown below.

Toxicity assessment

Parameter	Procedure
Clinical observations	Daily
Body weights	Weekly
Food consumption	Weekly
Gross pathology	At the end of the treatment (after 52 weeks) all animals were euthanized. A complete gross pathology examination was conducted.
Organ weights	The following organs from each animal were weighed: adrenals, heart, kidneys, liver, lungs, prostate, spleen, testes, and thyroids.
Histopathologic examinations	The following organs from all animals were examined histopathologically: adrenal gland, aorta, bone marrow, CNS, epididymis, gall bladder, heart, kidneys, large and small intestines, liver, lungs, lymph node (mesenteric and cervical), pancreas, pituitary gland, prostate gland, retina, salivary gland, skeletal muscle, peripheral nerve, skin, spleen, stomach, testis, thymus, thyroid gland, urinary bladder.

Results:

A. Clinical observations: Sporadic vomiting and sedation were present in the first 3 days. Slight equilibrium disturbance was noted in the first 3 days. No other treatment-related symptoms were observed thereafter.

B. Body weights and food consumption: Obviously increased body weight gain (5.5 kg) was noted in 1 dog. The sponsor claimed that the body weight gain from other dogs, together with food consumption was normal. **[Reviewer's comments**: No control data were provided. The sponsor indicated that the parameters were compared with historical control values. The body weight gain and food consumption were higher than those of the control animals in the 1-year toxicity study in dogs reported on February 27, 1976.]

C. Gross necropsy: Black concrements were found in bile (4/5) and dilated gall bladder (1/5). All animals had increased bile consistency. These changes were considered as treatment-related.

D. Organ weights: The relative and absolute weights of liver and thyroid glands were increased, while the weight of prostate glands was decreased.

E. Histopathology: Drug-induced changes were found only in livers. Hepatocyte swelling was noted in all animals. Granular cytoplasm and hyaline inclusion bodies were observed in 3/5 animals. No treatment-related, toxicologically significant changes were seen in gall bladder and urinary bladder.

In conclusion, male dogs were treated with HC 20-511 at 50 mg/kg/day for 1 year. Increased body weight gain, food consumption and liver weight were noted. Histopathological changes of liver were evidenced by hepatocyte swelling, granular cytoplasm and hyaline inclusion bodies. Increased bile consistency and concrements in bile or gall bladder were found in all treated animals. There were no signs of urolithiasis present, suggesting that the concrements in the urinary bladder could not be related to drug administration directly.

4. HC 20-511: 52 weeks peroral toxicity study in rhesus monkeys. Vol. 5

Project Nº: 151 Mo
Compound: HC 20-511
Route: Oral by stomach tube
Dose Level: 5 mg/ml/kg/day
Animal: Rhesus monkeys, 138-203 weeks old (males), 138-268 weeks old (females), 3/sex/group
Study Site:
Report Time: January 26, 1978
GLP/QAU: No

The purpose of this study was to evaluate the chronic toxicity of ketotifen in monkeys treated with HC 20-511 for 52 weeks. Toxicity was assessed as shown below.

Toxicity assessment

Parameter	Procedure
Clinical observations	Daily
Body weights	Weekly
Clinical pathology	Blood samples were collected from all animals prior to and 52 Weeks after the initiation of the treatment for blood chemistry and hematology examinations.
ECG	Prior to and 52 weeks after the initiation of the treatment
Ocular examinations	Ocular examinations (slit lamp and fundoscopy) were performed 51 weeks after the initiation of the treatment.
Laparotomy with vesicotomy	At the end of the treatment on 3 males and 2 females treated monkeys
Gross and histopathologic pathology	At the end of the treatment (after 52 weeks) on 1 female treated monkey

Results:

A. Clinical observations: From Week 41 one female treated animal (A12) had poor general condition including pilo-erection, exsiccosis, and stagnating body weight. During Week 44, the animal was transferred to another building for treatment. From Week 48, the animal was again incorporated into the study. The sponsor indicated that it was an intercurrent infection. In the other animals, no treatment-related changes were noted.

B. Body weights: Body weight changes are listed in the table below. Male monkeys receiving HC 20-511 showed a significant increase in body weight gain; while in females, the changes in treated and untreated animals were similar.

Body weight gain (%) in monkeys treated with HC 20-511 (n = 3)

	Body weight			
Dose	Starting to 26 weeks		Starting to 52 weeks	
(mg/kg/day)	♂	♀	♂	♀
0	5.7	6.1	18.6	18.0
5	17.4	5.4*	31.0	13.1*

* n = 2

C. Hematology: No treatment-related, toxicologically significant changes were noted.

D. Clinical chemistry: No drug-related differences were observed.

E. Eye examinations: No abnormal findings were noted.

F. ECG: No treatment-related differences were noted.

G. Laparotomy and vesicotomy: No urinary concrements were detected. The urinal bladders were normal.

H. Necropsy and histology: No treatment-related changes were noted in Animal A12.

In conclusion: Monkeys were treated with HC 20-511 at 5 mg/kg/day for a year. An increase in body weight gain was observed in male monkeys. No other drug-induced effects were noted. In urinary bladders, there was no concrement formation. A dose of 5 mg/kg/day was considered as NOAEL.

Ocular and local toxicity studies:

Studies reviewed:

1. 26-week local ocular tolerance and chronic toxicity study of DR 42013 by instillation into the conjunctival sac of rabbits (albino and pigmented). Vol. 11, Page 1.
2. HC 20-511: An eye irritation study in rabbits. Vol. 7
3. Ocular irritation study of ketotifen fumarate ophthalmic solution by one-time ocular instillation in rabbits. Vol. 7
4. Eye irritation study in rabbits after repeated doses of eye drops containing ketotifen fumarate. Vol. 7
5. A four-week eye toxicity study on ketotifen fumarate eye drops in rabbits. Vol. 7
6. A thirteen-week eye toxicity study on ketotifen fumarate eye drops in rabbits. Vol. 7
7. Quality test of ketotifen eye drops prepared in hospital. (2) The irritability test. Vol. 7
8. 13-week local ocular tolerance and subchronic toxicity study of heat-degraded DR 42013 by instillation into the conjunctival sac of albino rabbits. Vol. 8, Page 178.
9. Eye irritation study in rabbits after repeated doses of ketotifen fumarate eye drops of degraded quality. Vol. 7
10. Contact hypersensitivity to ketotifen base in albino guinea pigs. Vol. 7
11. HC 20-511: Local tolerance in the rabbit to intravenous administration of the ampoule solution. Vol. 7

Review:

1. 26-week local ocular tolerance and chronic toxicity study of DR 42013 by instillation into the conjunctival sac of rabbits (albino and pigmented). Vol. 11, Page 1.

Report Nº: 10868/97
Compound:
Route: Instillation into the conjunctiva sac of the right eye
Dosing Regimen: 25 µl/instillation, bid or qid x 26 weeks
Animal: New Zealand white rabbits (albino), 5-month old, 2.0-3.3 kg for males, 2.4-3.0 kg for females
Chinchilla Bastard rabbits (pigmented), 4-month old, 2.7-3.3 kg for males, 2.4-3.3 kg for females

Study Site: [redacted]

Study Duration: January 6 to July 8, 1998
Date of Final Report: October 12, 1998
GLP/QAU: Yes
Study Design:

Groups	Number of	N/sex
Albino rabbits	25 µl instillation/animal/day	
1 (Vehicle control)	Qid at 2-hr intervals	4
2 (KFSO)	Bid at 6-hr interval	4
3 (KFSO)	Qid at 2-hr intervals	4
Pigmented rabbits		
4 (Vehicle control)	Qid at 2-hr intervals	4
5 (KFSO)	Bid at 6-hr interval	4
6 (KFSO)	Qid at 2-hr intervals	4

The purpose of this study was to evaluate the local ocular tolerance and chronic toxicity of DR 42013 following daily ocular administration for 26 weeks in albino and pigmented rabbits. The day of first dosing was designated as Day 0. Toxicity was assessed as shown below.

Toxicity assessment for Study 10868/97

Parameter	Procedure
Clinical observations	At least once daily
Body weights	Weekly
Food and water consumption	Daily
Ophthalmologic examinations	Twice daily for conjunctivae. Ophthalmoscopic and fluorescein examinations were conducted on Days 0, 1, 15, 28, 56, 84, 112, 140, 168, 182 and 183. Examinations with slit lamp were performed on Days 0, 28, 84, 168 and 183.
Clinical pathology	Blood samples were collected prior to the first instillation on Day 0, and on days 28, 84 and 178 for hematology and clinical chemical examinations.
Urinalysis	Urine samples were collected before the treatment and on Days 28, 84 and 178.
Gross pathology	On Days 183 and 184, all animals were euthanized. A complete gross pathology examination was conducted.
Organ weights	The following organs from each animal were weighed: adrenal, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid.
Histopathologic examinations	The following organs from all animals were examined histopathologically: adrenal gland, aorta, bone (femur), bone marrow, brain, caecum, epididymis, esophagus, eyes, gall bladder, gross lesions, heart, kidney, large and small intestines, liver, lung, lymph node (cervical and mesenteric), mammary gland, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicle, skeletal muscle, sciatic nerve, skin, spinal cord, spleen, stomach, testis, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus and vagina.
Ocular histopathology	Left and right eyes from all animals were examined histologically.

Results:

A. Clinical observations: No treatment-related mortality and clinical signs were observed.