CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-157

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

Amendment to Chemistry Consult of 7/09/07

NDA No. 22-157
Sequence number/date/type of submission: 3/27/07, original
Sponsor and/or agent: UCB, Inc.
Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: Division of Pulmonary and Allergy Drug Products
Review completion date: 10/30/07.
Drug: levocetirizine

Amendment

The submission date was 3/27/07 (solution) and not 7/24/06 as indicated in the Chemistry consult request for the levocetirizine solution NDA22-157 submission.

In the review of 7/09/07 Chemistry consult that was finalized on 9/14/07, it was concluded that the exposure of the leachable, (b) (4) from the 15 ml and 150 ml (b) (4) bottles be (b) (4) 50 ug or be qualified to be acceptable. To support the exposure (b) (4) ug, the applicant cited a 76- week NOAEL (75 mg/kg) for a surrogate compound, (b) (4) which is structurally related to (b) (4) This NOAEL was used to calculate the allowable exposure to (b) (4) for a 6-year old and an adult.

The following calculations were used to determine the allowable exposure of the leachable, (b) (4) for a 6- year old and an adult.

The following data and factors were used in the calculations.

NOAEL in rat: 75 mg/kg, orally in a 76- week study
10: Unknown Factor (UF-A) to extrapolate from animals data to human data.
10: Unknown Factor (UF-H) to account for sensitive human sub-population.
10: Uncertainty factor (UF) regarding the uncertainty associated with the toxicity of the surrogate compound.
0.16: Conversion factor (CF) to account for differences in surface areas between rats and humans.

From the 75 mg/kg oral NOAEL, the Allowable Daily Dose (AD) exposure based on ug/kg =

$$\frac{\text{NOAEL x CF}}{\text{(UF-A x UF-H x UF)}} = \text{ug/kg}$$

$$\frac{75 \text{ mg/kg} \times 0.16}{10 \times 10 \times 10} = 12 \text{ ug/kg}$$

For a 25 kg 6 year old, the AD= 25 kg x 12 ug/kg = 300 ug

For a 50 kg ≥12 year old adult, the AD= 50 kg x 12 ug/kg = 600 ug

In reviewing the literature, there was an 80- week dietary study (Crampton et al, Toxicology 7 (3) 289, 1977) of BMT in female rats where the NOAEL was 4000 ppm (200 mg/kg).

From the 200 mg/kg NOAEL, the Allowable Daily Dose (AD) exposure using the above equation based on ug/kg=

$$\frac{200 \text{ mg/kg} \times 0.16}{10 \times 10 \times 10} = 32 \text{ ug/kg}$$

For 25 kg 6 year old, the AD= 25 kg x 32 ug/kg = 800 ug

For 50 kg ≥12 year old adult, the AD= 50 kg x 32 ug/kg = 1600 ug

Conclusion: The (b) (4) ug daily exposure of (b) (4) based on the leachable levels of (b) (4) ug/ml from a 15 ml capacity (b) (4) bottle and (b) (4) ug/ml from a 150 ml capacity (b) (4) bottle are acceptable for a 6- year old since the exposure was below allowable daily exposure of 300-800 ug based on two rat chronic oral toxicity studies. For adults (≥ 12 years old), the (b) (4) ug daily exposure of (b) (4) based on the same leachable levels is also acceptable since the exposure was also below the allowable daily exposure of 600-1600 ug based on the two rat chronic oral toxicity studies.

Recommendation: The daily exposures from 15 ml and 150 ml (b) (4) bottles of (b) (4) ug of (b) (4) (5 ml) to a 6 year old and of (b) (4) ug (10 ml) to an adult based on respective leachable levels of (b) (4) ug/ml are acceptable. This has been conveyed to the applicant in a telecon on October 9, 2007.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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/s/

Lawrence Sancilio
10/30/2007 03:10:37 PM
PHARMACOLOGIST

Joseph Sun
10/30/2007 03:24:26 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET
CHEMISTRY CONSULT

NDA number: 22-157
Date/type of submission: 1; 7/24/06, original
Sponsor and/or agent: UCB.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: **Division of Pulmonary and Allergy Drug Products**
Review completion date: 9/14/07

Drug:

Trade name: XYZAL
Generic name: levocetirizine
Code name: ucb 28556
Chemical name: 2-{(R)4[(4-chlorophenyl) phenylmethyl]-1-piperazinyl}ethoxy acetic acid dihydrochloride
CAS registry number: 130018-87-0

Drug class: H_1 receptor antagonist

Intended clinical population: Allergic patients.

Clinical formulation: Solution, 5 mg/10 ml in glass (b) (4) bottles.

Maximum Daily Dose: Children, 6-11 years old: (b) (4) Adults, ≥ 12 years old: 5 (b) (4)

Consult request by Craig Bertha, Ph.D. on the qualification of (b) (4) leachables and (b) (4) impurities/degradants in the XYZAL drug product.

Evaluation

There were (b) (4) leachables and (b) (4) impurities in the drug product requested in the consult. They are: (b) (4) the impurities were (b) (4) They were detected following 8 month storage at 40° C/75%relative humidity. They were identified from the peaks observed from gas chromatography. (b) (4) was identified twice in peaks (b) (4). From the 15 and 150 ml samples of glass (b) (4) bottles containing the drug product, the maximum amount of leachables extracted and the maximum amount impurity/leachable detected was used to determine maximum exposure. For qualification of the impurities (I) and leachables (L), the ICH Guidance

Qualification Threshold of 1% or 50 ug whichever is lower for the daily oral dose ≤ 10 mg is used.

The following table presents the maximum amount of impurities detected in the drug product and leachables extracted from the product in the 15 ml and 150 ml glass (b) (4) bottles The LOQs for (b) (4) were (b) (4) ppm and for Compound (b) (4) ppm. 1 ppm=1 ug/ml

Cpd. No./ Peak	**Compound**	**Origin in Product Drug or Bottle**	**Maximum Amount (ug/ml) Extracted From Product In Glass Bottle**	
			15 ml	**150 ml**
(b) (4)				

I-Impurity
L- Leachable
ND, LOQ was not specified

In the following table are the daily exposures of the leachables and impurities to 10 ml the drug product.

		(b) (4)	

Cpd. No./ Peak	Compound	Exposure (ug) to Impurity/Leachables From 10 ml Of Product 15 ml	150 ml	Exposure (ug) to Impurity/Leachables From 10 ml Of Product 15 ml	150 ml

(b) (4)

For the impurities, (b) (4) (CFR 21 182.60) are GRAS (b) (4) and (b) (4) is a food additive (CFR 21 172.515) and is present in several injectables; their exposures from the glass (b) (4) bottles are qualified. In the 15 and 150 ml glass bottles, the daily exposures to the leachables were qualified as they are below the ICH Guidance Qualification Threshold of 50 ug/day for a 5 mg daily dose. Not all the leachables in the (b) (4) bottles with the formulation are qualified. The exposures to (b) (4) in the 15 ml bottles and to (b) (4) in the 150 ml bottles (b) (4)

Overall Summary Conclusions and Recommendations

This was a consult for the qualification of the exposure of (b) (4) leachables and (b) (4) impurities in the drug product which consisted of 5 mg of levocetirizine/10 ml in 15 and 150 ml glass (b) (4) bottles. For safety, the ICH Guidance Qualification Threshold of 1% of the dose or 50 ug whichever is for lower a daily oral dose of ≤ 10 mg is used. The (b) (4) impurities are qualified as (b) (4) were in the GRAS category, and the third (b) (4) is a food additive. In the two glass containing products, exposures of the (b) (4) leachables are qualified. However, in the 15 ml and 150 ml (b) (4) containing product, the exposures for (b) (4) leachables (b) (4) in the 15 ml product and (b) (4) leachables (b) (4) in the 150 ml product are (b) (4)

Conclusion

The daily exposure of the (b) (4) impurities are qualified in the products in the glass (b) (4) bottles since they are GRAS or food additives; the (b) (4) leachables are below the ICH Guidance Qualification Threshold of (b) (4) ug for a 5 mg dose in the 15 and 150 ml product in the glass bottle and are qualified. The respective exposures of 3 and 2 leachables in the 15 and 150 ml product in the (b) (4) bottles are (b) (4)

Recommendation

The 5 mg/10 ml of levocetirizine may be dispensed in the 15 and 150 ml glass bottles and not in (b) (4) bottles unless the daily exposure to each of the leachables (b) (4) in the 15 ml (b) (4) bottle and to (b) (4) and (b) (4) in the 150 ml (b) (4) bottle is (b) (4) ug or qualified to be acceptable.

Reviewer's signature: _____

Supervisor's signature:

Concurrence - _____

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/s/

Lawrence Sancilio
9/13/2007 12:45:32 PM
PHARMACOLOGIST

Joseph Sun
9/13/2007 01:02:27 PM
PHARMACOLOGIST
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-157
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	3/27/07
PRODUCT:	levocetirizine
INTENDED CLINICAL POPULATION:	Allergy
SPONSOR:	UCB
DOCUMENTS REVIEWED:	Electronic submission
REVIEW DIVISION:	Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER:	Lawrence F. Sancilio, Ph.D.
PHARM/TOX SUPERVISOR:	Ching-long J. Sun, Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Lori Garcia

Date of review submission to Division File System (DFS): 8/21/07

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Recommend approval.

B. Recommendation for nonclinical studies
None.

C. Recommendations on labeling
None.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Levocetirizine is the R-enantiomer of cetirizine, a marketed H_1 receptor antagonist. In view of this, the long term toxicity, fertility and early developmental and prenatal postnatal developmental toxicity studies with cetirizine represent the toxicity profile of levocetirizine with supplemental bridging toxicity, and embryofetal developmental studies of levocetirizine.
In chronic oral toxicity studies in mice and rats with cetirizine, the liver was the target organ. The liver changes were enzyme induction and fat deposition. In Beagle dogs, targeted organ was the gastrointestinal system. The major clinical sign was emesis. In a dietary carcinogenicity study in rats, cetirizine was not tumorigenic, but the livers showed hypertrophy, vacuolation and fat deposition. In a dietary carcinogenicity study, male mice showed hepatic hypertrophy and benign liver tumors, the latter was due to enzyme induction. In mice, cetirizine did not affect fertility and early development and embryofetal development; in the prenatal and postnatal developmental study, there was lower pup weight. In embryofetal development studies in rats and rabbits, cetirizine was not teratogenic although increased skeletal anomalies/variants were observed in rabbits.
In a 4-week oral toxicity study in rats with levocetirizine, the target organ was the liver. There were hepatic hypertrophy and vacuolation, increased liver weight, induced liver enzymes and fat deposition. Enzyme induction in the rat is not toxicologically relevant.
In a 13-week oral toxicity study in rats with levocetirizine alone, the target organ again was the liver. There were hypertrophy and vacuolation, induced liver enzymes and fat deposition. A second 13-week oral toxicity study in rats was a bridging study with levocetirizine and cetirizine. Both compounds at comparable doses produced similar liver effects, increased enzymes, hypertrophy and central fat deposition.
In a 4-week oral toxicity study in dogs, a bridging study was made with cetirizine. At the HD dose, both levocetirizine and cetirizine were toxic putting the animals in a moribund condition which required a reduction in dose. Both compounds induced emesis and produced fecal impaction. The target organ was the gastrointestinal tract.

In a 13-week oral toxicity study in dogs, a bridging study was conducted with cetirizine. Both compounds produced emesis at comparable doses. Based on the toxicity studies in rats and dogs, there was no difference in the toxicity profile of levocetirizine and cetirizine.
Levocetirizine was not mutagenic in the Reverse Bacterial Mutation Assay and not genotoxic in the Mouse Lymphoma, Human Lymphocyte Chromosomal Aberration and Micronucleus Assays.
In a bridging Embryofetal Developmental study in rats and rabbits with levocetirizine and cetirizine, both compounds were not teratogenic although cetirizine did increase skeletal anomalies/variants in rabbits.

B. Pharmacology

Levocetirizine, the R-enantiomer of cetirizine is a potent and competitive H_1 receptor antagonist. In vitro H_1 receptor binding studies using different tissues, levocetirizine was 2-3 times more potent than cetirizine; in blocking the isolated guinea pig ileum and tracheal response to histamine, levocetirizine was 1-3 times more potent than cetirizine. In the in vivo histamine induced skin wheal assay in mice and rats, orally levocetirizine was 2-4 times more potent than cetirizine.

C. Nonclinical safety issues relevant to clinical use.

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

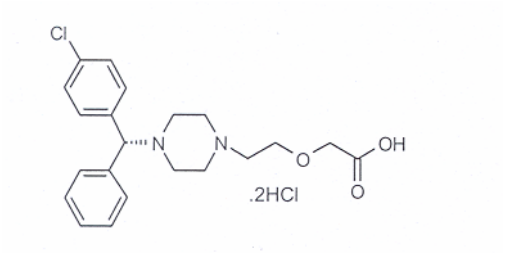
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-157
Review number: 1
Sequence number/date/type of submission: 3/27/07original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: UCB
Manufacturer for drug substance: UCB S.A.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: **Division of Pulmonary and Allergy Drug Products**
Review completion date: 8/20/07.

Drug:

Trade name: XYZAL
Generic name: levocetirizine
Code name: ucb 28556
Chemical name: 2-{(R) 4[(4-chlorophenyl) phenylmethyl]-1-piperazinyl} ethoxy acetic acid dihydrochloride
CAS registry number: 130018-87-0
Molecular formula/molecular weight: $C_{21}H_{25}N_2O_3Cl.HCl/461.8$
Structure:



Relevant INDs/NDAs/DMFs: NDA19-835, NDA 22-064

Drug class: H_1 receptor antagonist

Intended clinical population: Allergic patients.

Daily Dose: Adults, ≥ 12 years old: 5 mg; children, 6-11 years old, (b) (4).

Route of administration: Oral.

Clinical formulation: Solution, 0.5 mg/ml. The components are in the following table excerpted from the submission. All the excipients are acceptable.

Table 3:1 Proposed Commercial Formulation for Levocetirizine Dihydrochloride 0.5 mg/mL Oral Solution

Ingredient	Amount per mL (mg)	Function
Levocetirizine dihydrochloride	0.50	Active ingredient
Sodium acetate trihydrate, USP	(b) (4)	
Glacial acetic acid, USP		
Maltitol Solution, NF		
Glycerin (b) (4) USP		
Methylparaben, NF		
Propylparaben, NF		
Saccharin (b) (4)		
(b) (4)		
Purified water, USP		

Studies reviewed within this submission: None were submitted. The preclinical data is cross referenced to NDA 22-064. The review of NDA 22-064 is attached.

PHARMACOLOGY

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Refer to review of NDA 22-064**.**

2.6.2.2 Primary pharmacodynamics

Mechanism of action**:** Refer to review of NDA 22-064**.**

Drug activity related to proposed indication: Refer to review of NDA 22-064.

2.6.2.3 Secondary pharmacodynamics**:** Refer to review of NDA 22-064**.**

2.6.2.4 Safety pharmacology

Neurological effects: Refer to review of NDA 22-064**.**

Cardiovascular effects: Refer to review of NDA 22-064**.**

Pulmonary effects: Refer to review of NDA 22-064**.**

Renal effects**:** Refer to review of NDA 22-064**.**

Gastrointestinal effects: Refer to review of NDA 22-064**.**

Abuse liability: NA.

Other: NA.

2.6.2.5 Pharmacodynamic drug interactions: NA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Refer to review of NDA 22-064.

2.6.4.2 Methods of Analysis: NA.

2.6.4.3 Absorption: Refer to review of NDA 22-064.

2.6.4.4 Distribution: Refer to review of NDA 22-064.

2.6.4.5 Metabolism: Refer to review of NDA 22-064.

2.6.4.6 Excretion: Refer to review of NDA 22-064.

2.6.4.7 Pharmacokinetic drug interactions: NA.

2.6.4.8 Other Pharmacokinetic Studies: NA.

2.6.4.9 **Discussion and Conclusions:** Refer to review of NDA 22-064.

2.6.4.10 Tables and figures to include comparative TK summary: NA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary Refer to review of NDA 22-064**.**

General toxicology: Refer to review of NDA 22-064**.**

Genetic toxicology: Refer to review of NDA 22-064.

Carcinogenicity: Refer to review of NDA 22-064**.**

Reproductive toxicology: Refer to review of NDA 22-064**.**

Special toxicology: Refer to review of NDA 22-064.

2.6.6.2 Single-dose toxicity: Refer to review of NDA 22-064.

2.6.6.3 Repeat-dose toxicity: Refer to review of NDA 22-064**.**

2.6.6.4 Genetic toxicology: Refer to review of NDA 22-064**.**

2.6.6.5 Carcinogenicity: Refer to review of NDA 22-064**.**

2.6.6.6 Reproductive and developmental toxicology: Refer to review of NDA 22-064**.**

2.6.6.7 Local tolerance: NA.

2.6.6.8 Special toxicology studies: Refer to review of NDA 22-064.

2.6.6.9 Discussion and Conclusions: Refer to review of NDA 22-064.

2.6.6.10 Tables and Figures: NA.

2.6.7 TOXICOLOGY TABULATED SUMMARY: NA**.**

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Levocetirizine is the R-enantiomer of the marketed cetirizine. The long term oral toxicity, fertility and early developmental and prenatal postnatal developmental toxicity studies with cetirizine represent the toxicity profile of levocetirizine with supplemental bridging toxicity, developmental and genotoxicity studies conducted with levocetirizine.

Cetirizine

In acute intravenous toxicity study in the mouse, toxicity and lethality were seen at 320 mg/kg. The toxic signs were unsteady gait, dyspnea, decreased motor activity, jerks, side lying paddling movements, tremors; deaths occurred within 6 days and at 420 mg/kg, all mice died within 10 min following administration.
In chronic toxicity studies in mice and rats with cetirizine, the liver was the target organ, in males. The liver changes were the result of enzyme induction and were reversible. Livers also showed fat deposition. In Beagle dogs, the targeted organ was the gastrointestinal tract. The clinical signs depending on the dose were emesis, salivation, tremors, quiet behavior, ataxia and hypothermia, loose mucus feces. In the carcinogenicity studies in rodents, the dietary doses were 1, 4 and 16 mg/kg for the mouse and 3, 8 and 20 mg/kg for the rat. The rats showed liver toxicity (hypertrophy,

vacuolation and fat deposit). No tumors were seen in rats that were clinically significant, while male mice showed benign liver tumors which were due to enzyme induction.
In genotoxicity studies, cetirizine was negative in the Ames, Human Peripheral Lymphocytes Chromosomal Aberration, Mouse Lymphoma and Mouse Micronucleus assays.
In reproductive toxicity studies with cetirizine, mice were used in the Fertility and Early Development (4, 16, 64 mg/kg), Embryofetal Developmental (6, 24, 96 mg/kg) and Prenatal and Postnatal Development studies (6, 24, 96 mg/kg). There was no effect on fertility, but increased skeletal anomalies/variants (MD, HD) in the fertility and early developmental study and no effect in the embryofetal developmental study. In the prenatal and postnatal development study, there was at the HD decreased pup weight. In rabbits, cetirizine at 75 mg/kg orally, did not affect embryofetal development.
In rats, cetirizine at oral doses of 5, 30 and 200 mg/kg were tested in both sexes in the fertility and early developmental studies. Cetirizine did not affect sperm dynamics, fertility and early fetal developmental.

Levocetirizine

Studies show that levocetirizine was a competitive inhibitor of the H_1 receptor. In in vitro binding studies, levocetirizine was more potent (1-4 x) than cetirizine. Levocetirizine was 2 times as potent as cetirizine in inhibiting the binding to the human H_1 receptors (Ki: 3nM vs. 6 nM). In the in vitro tracheal and isolated guinea pig ileum preparations, levocetirizine antagonized histamine-induced contractions. In these studies levocetirizine was 2-4 x more potent than cetirizine. In an in vivo preparations, levocetirizine intravenously inhibited histamine induced bronchospasms in anesthetized guinea pigs that was twice that of cetirizine. In inhibiting the histamine induced wheal test in mice and rats, levocetirizine was 2-4 times more potent than cetirizine and in dogs, the activity of levocetirizine 0.15 mg/kg was more active than cetirizine (58% vs.48%). In all studies levocetirizine and cetirizine were more potent than S-cetirizine. The in vitro antihistaminic activity of levocetirizine was 9 times more potent that P026, a metabolite of cetirizine.
The activity of levocetirizine was weak in inhibiting the binding of 12 other radioligands.
Safety Pharmacology studies were conducted with levocetirizine in mice, rats and dogs. A single oral (46, 138, 462 and 1384 mg/kg) and intraperitoneal (14, 46, 92 and 138 mg/kg) dose study was conducted in mice, By the oral route, tremors piloerection, decreased motor activity and muscle tone were seen initially at 138 mg/kg and progressed until death at 462 mg/kg. By the intraperitoneal route, these changes began at 46 mg/kg and progressed until death at 138 mg/kg. In rats, doses of 25, 50 and 100 mg/kg, orally levocetirizine produced no central nervous system depression as determined by the Irwin test. In mice, levocetirizine potentiated hexobarbital sleeping time and in rats did not affect pentobarbital sleeping time. Levocetirizine did not show significant central nervous system effects.
In evaluating the effect on the cardiovascular system, in vitro and in vivo studies were conducted. In the Xenopus laveis oocytes hERG K+ assay, both levocetirizine and cetirizine were inactive at 30 uM, but in the guinea pig K+ current effects using ventricular myocytes assay blockage by both levocetirizine and cetirizine were equally

effective at 0.1 mM showing comparable activity. Levocetirizine at 30 and 300 uM (both are high concentrations) inhibited the potassium channel by prolonging the action potential duration of the dog isolated Purkinje fibers and did not affect the maximal diastolic potential (MDP), action amplitude amplitude (APA) and the maximum upstroke velocity of phase 0 of the action potential (Vmax). Since levocetirizine did not affect the maximum upstroke velocity indicates that the sodium channel was not affected. In anesthetized rats, levocetirizine at intravenous doses of up to 25.9 mg/kg produced a transient decrease in diastolic pressure and heart rate. In anesthetized dogs, cumulative intravenous doses starting at 4.6 mg/kg and ending at 138.2 mg/kg produced bradycardia at 4.6 mg/kg; at doses ≥ 46.2 mg/kg, there were transient tachycardia, disturbance of conduction and repolarization and death. In another study, levocetirizine at cumulative intravenous doses up to 10 mg/kg in anesthetized dogs did not affect the cardiovascular and respiratory systems. In a gastrointestinal study in rats, levocetirizine at oral doses up to 100 mg/kg did not affect gastrointestinal transit time.

In distribution studies in rats, the highest concentrations were seen in the liver, kidney, pancreas and gastrointestinal tract. Radioactivity in the placenta, fetus and brain were less than background. In dogs, the highest concentration was in the bile, liver and kidneys. The brain shows levels that were 12% of plasma level and 19% of the blood level. However, the average ratio of tissue radioactivity in the brain to plasma unbound levocetirizine levels was 2.8 at 24 hours post dose. In rats, the main metabolites were M1, M2, F11 and F12. In dogs, the major metabolites were M7+M8 (16-23% of the dose) and M10 (8-13% of the dose) along with unchanged levocetirizine.

In acute toxicity studies, there was no difference in the toxicities between levocetirizine and cetirizine.

Multidose oral toxicity studies of 4-and 13- weeks were conducted in rats and dogs.

In a 4-week study in rats, the toxicity of levocetirizine and S-cetirizine at the same doses showed a similar toxicity profile with hepatic centrilobular and midzonal enlargement, increase liver enzymes, hepatic centrilobular and midzonal fat and hepatic vacuolation. The liver enzyme increases were due to enzyme induction. The target organ was the liver. All the changes were reversible.

In a 13-week oral toxicity study in rats, only salivation was the clinical sign. Males showed an increase in central lobular vacuolation central fat deposition and increased liver enzymes. The target organ was the liver. All the changes were reversible.

In a second 13-week oral toxicity study in rats with levocetirizine, cetirizine was included. Both compounds induced enzymes and hepatic fat deposition. The target organ was the liver; both compounds showed a similar toxicity profile.

Two 4-week and two 13-week oral toxicity studies were conducted in dogs. In the first 4-week study both levocetirizine and S-cetirizine; levocetirizine was toxic and lethal at the HD requiring the dose to be lowered to 90 mg/kg on day 8.The HD of S-cetirizine showed only emesis and hypersalivation; in addition, the levocetirizine treated animals showed tremors and instability. Significant increase in the incidence of emesis occurred at the MD and HD for both compounds, a toxicity common for both enantiomers. At the HD, both compounds produced increased urine volume. The target organ was the gastrointestinal tract for both compounds.

In the second 4-week oral study in dogs, the test compounds were levocetirizine, S-cetirizine and cetirizine. Two female HD levocetirizine treated animals were killed in a

moribund condition which was treatment related. For S- cetirizine 2 HD females were killed in a moribund condition and 1 MD female died due to bronchopneumonia resulting from aspiration of the vomitus. The HD of levocetirizine and cetirizine were reduced to 90 mg/kg from days 11/18. Emesis was seen at all doses of the 3 compounds. There was a 15% increase in the Qtc interval in the levocetirizine treated animals which was not confirmed. Fecal impaction was seen at the MD and HD levocetirizine and in the cetirizine treated animals and not in the S-cetirizine treated animals. Histopathology seen in the trachea of levocetirizine and S-cetirizine treated animals was not confirmed in another 4-week oral study at the same dose. The target organ was the gastrointestinal tract, and all the changes were reversible.

In a 13-week oral toxicity study in dogs, levocetirizine caused increased incidence of emesis occurred in the HD males and in all the doses in females showing increased sensitivity. The targeted organ of toxicity was the gastrointestinal tract and the findings were reversible.

In the second oral 13-week toxicity study in dogs, the toxicity of levocetirizine and cetirizine was compared. Both induced emesis at the doses tested. At week 13, there was at 75 mg/kg of levocetirizine and cetirizine a 7% increase in Qtc in females. This low increase is not of clinical concern. Further, the increased Qtc with levocetirizine was not confirmed at the same dose in the other 13-week study. The changes in hematological, clinical chemistry, liver and salivary weight changes and histological changes in the testes and liver were not treatment related since they were not confirmed in another 13-week study. The gastrointestinal tract was the target organ of toxicity. Both compounds showed a similar toxicity profile.

Levocetirizine was not mutagenic in the Reverse Bacterial Mutation assay and not genotoxic in Mouse Lymphoma assay and in one Micronucleus assay. Six Human Lymphocyte Aberration assays were conducted. The conclusion was that levocetirizine was not genotoxic. This was based on a positive response that was not confirmed or the positive response occurred at an excessive cytotoxic concentration and lower concentrations were negative.

In fertility and early developmental studies in rats, cetirizine at oral doses up to 200 mg/kg were tested in both sexes. Cetirizine did not affect sperm dynamics, female fertility and early fetal developmental.

Embryofetal developmental studies were conducted in rats and rabbits. In pregnant rats, oral doses of 50, 100 and 200 mg/kg of levocetirizine and 200 mg/kg of cetirizine were tested. Levocetirizine and cetirizine did not produce skeletal and visceral malformations, anomalies or skeletal variants. In an embryofetal development study in rabbits, levocetirizine at 30, 60 and 120 mg/kg, orally and cetirizine at 120 mg/kg, orally were not teratogenic. However, cetirizine produced a slight increase in the incidence of skeletal variants.

Conclusion

The toxicity profile of levocetirizine and cetirizine was similar.

Unresolved toxicology issues (if any): None.

Recommendation:

Approval of NDA 22-157.

Suggested labeling: None.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-064
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	7/24/06
PRODUCT:	levocetirizine
INTENDED CLINICAL POPULATION:	Allergy
SPONSOR:	UCB
DOCUMENTS REVIEWED:	Electronic submission
REVIEW DIVISION:	Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER:	Lawrence F. Sancilio, Ph.D.
PHARM/TOX SUPERVISOR:	Ching-long J. Sun, Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Lori Garcia

Date of review submission to Division File System (DFS): 5/8/07

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EXECUTIVE SUMMARY

II. Recommendations

D. Recommendation on approvability
Recommend approval.

E. Recommendation for nonclinical studies
None.

F. Recommendations on labeling
Modify the submitted label as recommended.

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II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Levocetirizine is the R-enantiomer of cetirizine, a marketed H_1 receptor antagonist. In view of this, the long term toxicity, fertility and early developmental and prenatal postnatal developmental toxicity studies with cetirizine represent the toxicity profile of levocetirizine with supplemental bridging toxicity, and embryofetal developmental studies of levocetirizine.

In chronic oral toxicity studies in mice and rats with cetirizine, the liver was the target organ. The liver changes were enzyme induction and fat deposition. In Beagle dogs, targeted organ was the gastrointestinal system. The major clinical sign was emesis. In a dietary carcinogenicity study in rats, cetirizine was not tumorigenic, but the livers showed hypertrophy, vacuolation and fat deposition. In a dietary carcinogenicity study, male mice showed hepatic hypertrophy and benign liver tumors, the latter was due to enzyme induction. In mice, cetirizine did not affect fertility and early development and embryofetal development; in the prenatal and postnatal developmental study, there was lower pup weight. In embryofetal development studies in rats and rabbits, cetirizine was not teratogenic although increased skeletal anomalies/variants were observed in rabbits.

In a 4-week oral toxicity study in rats with levocetirizine, the target organ was the liver. There were hepatic hypertrophy and vacuolation, increased liver weight, induced liver enzymes and fat deposition. Enzyme induction in the rat is not toxicologically relevant.

In a 13-week oral toxicity study in rats with levocetirizine alone, the target organ again was the liver. There were hypertrophy and vacuolation, induced liver enzymes and fat deposition. A second 13-week oral toxicity study in rats was a bridging study with levocetirizine and cetirizine. Both compounds at comparable doses produced similar liver effects, increased enzymes, hypertrophy and central fat deposition.

In a 4-week oral toxicity study in dogs, a bridging study was made with cetirizine. At the HD dose, both levocetirizine and cetirizine were toxic putting the animals in a moribund condition which required a reduction in dose. Both compounds induced emesis and produced fecal impaction. The target organ was the gastrointestinal tract.

In a 13-week oral toxicity study in dogs, a bridging study was conducted with cetirizine. Both compounds produced emesis at comparable doses. Based on the toxicity studies in rats and dogs, there was no difference in the toxicity profile of levocetirizine and cetirizine.
Levocetirizine was not mutagenic in the Reverse Bacterial Mutation Assay and not genotoxic in the Mouse Lymphoma, Human Lymphocyte Chromosomal Aberration and Micronucleus Assays.
In a bridging Embryofetal Developmental study in rats and rabbits with levocetirizine and cetirizine, both compounds were not teratogenic although cetirizine did increase skeletal anomalies/variants in rabbits.

B. Pharmacology

Levocetirizine, the R-enantiomer of cetirizine is a potent and competitive H_1 receptor antagonist. In vitro H_1 receptor binding studies using different tissues, levocetirizine was 2-3 times more potent than cetirizine; in blocking the isolated guinea pig ileum and tracheal response to histamine, levocetirizine was 1-3 times more potent than cetirizine. In the in vivo histamine induced skin wheal assay in mice and rats, orally levocetirizine was 2-4 times more potent than cetirizine.

C. Nonclinical safety issues relevant to clinical use.

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

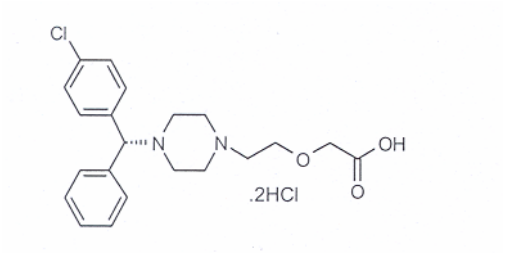
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-064
Review number: 1
Sequence number/date/type of submission: 7/24/05/original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: UCB
Manufacturer for drug substance: UCB S.A.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: **Division of Pulmonary and Allergy Drug Products**
Review completion date: 8/15/07

Drug:

Trade name: XYZAL
Generic name: levocetirizine
Code name: ucb 28556
Chemical name: 2-{(R) 4[(4-chlorophenyl) phenylmethyl]-1-piperazinyl} ethoxy acetic acid dihydrochloride
CAS registry number: 130018-87-0
Molecular formula/molecular weight: $C_{21}H_{25}N_2O_3Cl.HCl/461.8$
Structure:



Relevant INDs/NDAs/DMFs: NDA 19-835

Drug class: H_1 receptor antagonist

Intended clinical population: Allergic patients.

Clinical formulation: 5 mg tablets.

Daily Dose: Adults, ≥ 12 years old: 5 mg; children, 6-11 years old, (b) (4)

Route of administration: Oral.

Studies reviewed within this submission

PHARMACOLOGY

Primary Pharmacodynamics

Mechanism of action

Inhibition of levocetirizine and S-cetirizine of [^{3}H] mepyramine binding to the cerebral cortex of mice, No. RRLE95A0510

Binding of levocetirizine and S-cetirizine to human H_1 receptors; comparison with cetirizine, No. RRLE95M1801.

Affinity and selectivity of levocetirizine and S-cetirizine and cetirizine for human H_1 receptors, No. RRLE96A1901.

H1 antagonists: Receptor affinity vs. selectivity, No. ADPE03B1704.

Binding characteristics of cetirizine and levocetirizine to human H_1 receptors: contribution of LYS and THR, No. ADPE02A3102.

Binding characteristics of [^{3}H] levocetirizine to cloned human H_1-histamine receptors expressed in CHO cells, No. ADPE02A1404.

Histamine H_1 receptor activation of nuclear factor B: roles for G- and G q/11 subunits in constitutive and agonist-mediated, No. ADPE02B2701.

Antihistaminic properties of levocetirizine and S-cetirizine in the in vitro guinea pig isolated trachea assay, No.RRLE92E2004.

Activity of levocetirizine and S--cetirizine on contraction of the isolated guinea pig induced by acetylcholine, serotonin, histamine and nicotine, No. RRLE92E2003.

Effect of cetirizine and its enantiomers on histamine-induced contraction of the isolated guinea pig trachea, No. RRLE98J2801.

Effect of cetirizine and its enantiomers on histamine-induced contraction of the isolated guinea pig ileum, No. RRLE97G1803.

Generalized behavioral effects and antihistaminic activity of cetirizine, levocetirizine and S-cetirizine, No. LE88B242.

Effect of levocetirizine and S-cetirizine on respiratory spasms induced in the guinea pig, No. RRLE95A0511.

Pharmacodynamics kinetics of cetirizine and its enantiomers on histamine-induced bronchospasms in anesthetized crurarized guinea pigs. No. RRLE95G1801

Effect of levocetirizine and S-cetirizine on the wheal response to histamine in mice, No. RRLE95A0509.

Effect of levocetirizine and S-cetirizine on the wheal response to histamine in mice, No. RRLE95E2091.

Effect of levocetirizine and S-cetirizine on the wheal response to histamine in rats, No. RRLE95 A0502 with addendum.

Effect of levocetirizine and S-cetirizine on the wheal response to histamine in dogs, No. RRLE95A0504 with amendment.

Effect of cetirizine and its enantiomers on histamine-induced wheal response in dogs, No. RRLE95A1202.

Antihistamine activities and general pharmacological studies of P026, a metabolite of cetirizine, No. RXLE94E2705.

Secondary Pharmacodynamics

Activity and selectivity profile of cetirizine, levocetirizine and S-cetirizine for human H_1 receptors, No. RRLE96A1901.

Safety Pharmacology

Effect of cetirizine and its enantiomers, levocetirizine and S-cetirizine, on the general behavior and antihistaminic activity in mice, No. LE88B242.
Effect of oral and intraperitoneal levocetirizine on the general behavior in mice, No. RRLE92E0508.
Effect of levocetirizine on hexobarbital induced sleeping time in mice, No. RRLE95A0505.
Effect of cetirizine, levocetirizine and S-cetirizine, on the hexobarbital induced sleeping time in mice, No. RRLE93D2901.
Effect of levocetirizine and cetirizine on general activity and behavior (Irwin Test) in rats, No. RRLE99A1104
Effect of cetirizine and levocetirizine on the general locomotor activity of rats, No. RRLE99A1105.
Effect of cetirizine and levocetirizine on pentobarbital sleeping time in rats, No. RRLE99A1106.

Cardiovascular

Effect of levocetirizine and cetirizine on the Xenopus laveis oocytes hERG K^+ assay, No. RRLE99B1801.
Effect of Levocetirizine, cetirizine and S-cetirizine on the guinea pig K+ current effects using ventricular myocytes assay, No. ADPE98G0201.
Effect of cetirizine, levocetirizine and dextrocetirizine on the action potentials of canine cardiac Purkinje fibers, No. RRLE98H1102.
Hemodynamic effect of levocetirizine in anesthetized Sprague Dawley rats, No. RRLE95A0507.
Acute circulatory tolerance of cumulative intravenous doses of levocetirizine in anesthetized dogs, No. RRLE93H0901.
Effect of levocetirizine on cardiac rhythm in a model of acquired long QT syndrome in halothane anesthetized dogs, No. RRLE99H1105.
Effect of intravenous levocetirizine on the cardiovascular and respiratory systems in anesthetized dogs, No. RRLE96K0402.

Respiratory

Effect of intravenous levocetirizine on the cardiovascular and respiratory systems in anesthetized dogs, No. RRLE96K0402.

Gastrointestinal

Effect of cetirizine and levocetirizine on gastrointestinal transit in rats, No. RRLE99A1107.

PHARMACOKINETICS/TOXICOKINETICS

PHARMACOKINETICS

Absorption

Comparative pharmacokinetics in Beagle dogs, No.LE88B021
Absorption distribution, metabolism and elimination of [^{14}C] levocetirizine after oral administration to Beagle dogs, No. RRLE99L1301
Characterization of the transport through the CACO-2 (HTB-37), No. RLE02A2403

Distribution

Absorption distribution, metabolism and elimination of [^{14}C] levocetirizine after oral administration to Beagle dogs, No. RRLE99L1301
Tissue distribution of total radioactivity following a single oral dose of [^{14}C] levocetirizine, No. RRLE99G1401

Metabolism

Metabolism and pharmacokinetics [^{14}C] levocetirizine in rats following a single oral administration by gavage, No. RRLE95H0901
Preliminary in vitro metabolism using rat liver fractions, No. RRLE99E1001
Metabolites of [^{14}C] levocetirizine following a single oral dose in rats, No. RRLE00C1503

Excretion

Retention and balance of excretion of [^{14}C] levocetirizine in rats following a single oral dose, No. RRLE97C0601

TOXICOLOGY

Single-dose toxicity

Acute oral toxicity of levocetirizine in the mouse, No. RRLE92C1003
Acute intravenous toxicity of levocetirizine in the mouse, No. RRLE92E1301
Acute intravenous toxicity of levocetirizine, S-cetirizine and cetirizine in the mouse, No. RRLE87E131
Acute oral toxicity of levocetirizine in the rat, No. RRLE92D2104
Acute intravenous toxicity of levocetirizine in the rat, No. RRLE92F0303
Acute oral toxicity of levocetirizine in the dog, No. RRLE92C1202

Repeat-dose toxicity

4-Week oral toxicity in the rat, No. RRLE95C1401 (TX001).
13-Week oral toxicity in rats of levocetirizine with a 4-week, recovery period, No. No. RRLE92G0902 (UCB412).
13-Week oral toxicity in rats of levocetirizine compared with cetirizine with a 4-week, recovery period, No. RRLE98H2402 (TA0283).
Lymphocyte subset counts in rats from the 13-Week oral toxicity, No. RRLE98H2403.
4-Week oral toxicity of levocetirizine in the dog, No. RRLE95C2004 (TX002)
4-Week oral toxicity of cetirizine, levocetirizine and S- cetirizine in the dog, No. RRLE99L1401 (TX008)
13-Week oral toxicity in dogs of levocetirizine, No. RRLE92G1003(UCB413)
13-Week oral toxicity in dogs of levocetirizine compared with cetirizine with a 4-week, recovery period, No. RRLE97F0201(TX282).

Genetic Toxicology

Reverse bacterial mutation assay RRLE99K1101
Reverse bacterial mutation assay, No. RRLE92B1303
Micronucleus assay in mice, No. RRLE92F1501
Chromosome Aberration assay inhuman lymphocytes (Batch D011), No.RRLE95K0202
Chromosome Aberration assay inhuman lymphocytes (Batch D005), No.RRLE92F505
Analysis of chromosomal aberrations in metaphase cells of human peripheral lymphocytes culture, No. RRLE95L2807. Note this is a review of the slides from

report No.RRLE92F505 using Batch No. D005
Chromosome Aberration assay inhuman lymphocytes (Batch D008), No.RRLE92G1503
Chromosome Aberration assay inhuman lymphocytes (Batch 05B201020), No.RRLE06B1736
Human lymphocyte metaphase analysis, No. RRLE95G1101
Chromosome Aberration assay in human lymphocytes (Batch D008), No. RPLE95K0203
Mouse lymphoma test in mice, No**.** RRLE99K1102
Mouse lymphoma test in mice, No**.** RRLE92D0804

Reproductive and developmental toxicology

Reproductive and developmental studies with cetirizine in rats, No. ARLE00C1001

Embryofetal development

The effect on embryofetal development in rats from oral administration of levocetirizine and cetirizine, No. RRLE93F3001
The effect on embryofetal development in rabbits from oral administration of levocetirizine and cetirizine, No. RRLE93C005

Special Toxicology Studies

Cytotoxicity of levocetirizine, S-cetirizine and cetirizine on primary cultures of rat hepatocytes, No. RRLE95L0502.

Studies <u>not</u> reviewed within this submission:

The following reports were related to cetirizine and terfenadine.

Histamine H_1 receptor antagonism by cetirizine in isolated guinea pig tissues: influence of receptor reserve and dissociation kinetics, No. ADPE03F0305.
Effect of cetirizine on the human ether-a-gogo related gene (HERG) product, a cardiac K^+ channel, No. TB0441.
Effect of cetirizine and terfenadine on the delayed K^+ currents cardiac cells, No. APDE98G0201.

The following were published articles.

Inhibition by cetirizine and levocetirizine on eotaxin-induced eosinophil transendothelial migration through human dermal or lung microvascular endothelial cells, No. ADPE02J0203.
H_1 receptor mediated inflammatory responses in human keratinocytes, No. ADPE04L2201.

Inhibition by levocetirizine of VCAM-1expression on human dermal endothelial cells, No. ADPE03K3101.
Effects of levocetirizine on histamine and cytokine-induced upregulation of eotaxin by endothelial cells, No. ADOE02G1007.

The following report was not reviewed as it was not relevant to the NDA.

Metaphase chromosome analysis comparison of effects in the presence of S9 preparations from different species, No. RRLE000902**.**

The following reports were not reviewed since they do not add information impacting on the approval of the NDA.

The molecular basis for the lack of cardiovascular side effects of cetirizine. Studies on the Human Ether-A-GoGO related gene (HERG) product, No. RLLE99B1801.
Cytotoxicity of human lymphocytes with levocetirizine, cetirizine, and S-cetirizine, No. RRLE95K021. Note: This was not part of the Chromosome aberration assay.
Cytotoxicity of human lymphocytes with levocetirizine, cetirizine, and S-cetirizine after 3 hr treatment in the presence of S9, No. RRLE99C2601 Note: This was not part of the Chromosome aberration assay.
Report of levocetirizine, cetirizine, and S-cetirizine in the determination of ALP and inorganic phosphorous in the plasma of dogs, No. RRLE99E1803
In vitro study on the interference of levocetirizine, cetirizine, and S-cetirizine on protein and bile salts levels determination in urine of rats and dogs, No. RRLE99E1801

The following reports on P026 were not reviewed since P026 (UCB26026) is the metabolite, O-dealkylated levocetirizine, present at low level relative to levocetirizine in rats, dogs and humans. In humans, the Cmax of P026 ranged from 11-47 ng/ml (mean: 20 ng/ml) and the mean of levocetirizine was 308 ng/ml.

Acute oral toxicity in the mouse, No. LE89G284
Acute intravenous toxicity in the mouse, No. LE89G282
Acute oral toxicity in the rat, No. LE89G285
Acute intravenous toxicity in the rat, No. LE89G283

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Levocetirizine is the R-enantiomer of cetirizine, an H_1 receptor antagonist. It is a selective inhibitor of the H_1 receptor. Its antihistamine activity in in vitro and in vivo studies showed that is was more potent or equipotent to cetirizine and more potent than S-cetirizine. Its potent activity was demonstrated in several in vitro binding studies: inhibition of mepyramine binding in the mouse cerebral cortex (IC50: levocetirizine, 12

nM; S-cetirizine, 310 nM; cetirizine, 27 nM) and inhibition of mepyramine binding to the human H_1 receptor expressed in CHO cells (Ki: 2-3 nM: S-cetirizine: 80 nM; cetirizine, 6 nM). The dissociation t1/2 of levocetirizine and cetirizine were similar (levocetirizine: 115± 38 min; cetirizine: 95± 33 min) Levocetirizine binds competitively to the H_1 receptor and its high affinity is due to interaction with lysine of the receptor and its stereoselectivity is in part to the Threonine^{194} portion of the histamine binding site. Levocetirizine affinity to the NF-kB (a pro-inflammatory transcriptin) activity in transfected COS-7 cells was more potent than the S-cetirizine (Ki 16 nM vs. 160 nM).
In the in vitro isolated guinea pig tracheal and ileum preparations, levocetirizine antagonized histamine-induced contractions. In the trachea preparation, the IC50 was 31 nM as compared to 62 nM for cetirizine, and in another study, the respective pA2 values were 7.9 and 7.3 for levocetirizine and cetirizine indicating that levocetirizine was more potent than cetirizine. In the ileum preparation, at 5 min incubation, the IC50s were 2 uM indicating that levocetirizine and cetirizine were equipotent; when the incubation time was increased to 60 min, levocetirizine was more potent than cetirizine (pA2 of 8.3 for levocetirizine and 8.0 for cetirizine) indicating that the potency of levocetirizine increased with exposure. At 0.15 mg/kg intravenously to anesthetized guinea pigs, the maximum inhibition of histamine induced bronchial spasms by levocetirizine (98%) was greater than cetirizine (45%). In the histamine-induced skin wheal test, levocetirizine was more potent than cetirizine in mice, rats and dogs. In mice, the respective oral ED50 was 0.018 mg/kg and 0.073 mg/kg for levocetirizine and cetirizine. In rats, the respective oral ED50s were 0.9 mg/kg and 2 mg/kg for levocetirizine and cetirizine. In a crossover study in dogs, at 0.15 mg/kg orally, the maximum inhibition of histamine induced wheal by levocetirizine was 58% as compared to 48% for cetirizine. In another oral study in dogs, 0.32 mg/kg of levocetirizine inhibited the wheal response by 76% as compared to 49% for 3.2 mg/kg of S-cetirizine. In unanesthetized guinea pigs, the intravenous ED50 for P026, a metabolite of cetirizine, was 3 mg/kg for blocking histamine induced bronchospasms. In an in vitro study, the IC50 of P026 for blocking histamine induced contraction of guinea pig ileum was 18 uM indicating that it was less potent than levocetirizine and cetirizine with IC50s of 2 uM.
In a secondary pharmacodynamics study, the binding selectivity of levocetirizine was undertaken. At 10 umol/l, a concentration well beyond the maximum antihistaminic dose for levocetirizine and cetirizine, the antihistamine inhibition for the 2 compounds was 100% while at the same concentration, the activity of levocetirizine in inhibiting the binding of 12 other radioligands ranged from -2% to 82%.
Safety Pharmacology studies were conducted with levocetirizine in mice, rats and dogs. In a single dose study in mice, levocetirizine was administered by the intraperitoneal (14, 46, 92 and 138 mg/kg) and oral (46, 138, 462 and 1384 mg/kg) routes to determine behavioral changes. By the intraperitoneal route, piloerection, decreased motor activity and muscle tone were seen initially seen 46 mg/kg. This progressed to tremors and cyanosis at 138 mg/kg and death within 24 hr. By the oral route, similar observations in addition to reddening of the skin were seen at 138 mg/kg. Death occurred at 462 mg/kg. These changes were confirmed in second intraperitoneal and oral studies in mice. The effect on hexobarbital sleeping time was determined at 25.9, 46.2 and 83.1 mg/kg, intraperitoneally. Increased duration of sleeping time occurred at 83.1 mg/kg (C: 2.8 min vs. 18.1 min). In rats, doses of 25, 50 and 100 mg/kg, orally did not affect locomotor

activity over a 2-hr period following administration. In subsequent studies at the same doses, levocetirizine produced no central nervous system depression as determined by the Irwin test and did not increase the duration of pentobarbital sleeping time.
In evaluating the effect on the cardiovascular system, in vitro and in vivo studies were conducted. In the Xenopus laveis oocytes hERG K^+ assay, both levocetirizine and cetirizine were inactive at 30 uM. However, in the guinea pig K^+ current assay using ventricular myocytes assay, at 0.1 mM, blockage of the current was 55% for levocetirizine, 51 % for cetirizine and 35% for S-cetirizine. This indicated that levocetirizine and cetirizine possessed comparable activity, and both compounds were more active than S-cetirizine. Levocetirizine at 30 and 300 uM prolonged the action potential duration 50, 70 and 90 of the dog isolated Purkinje fibers. Levocetirizine did not affect the maximal diastolic potential (MDP), action amplitude amplitude (APA) and the maximum upstroke velocity of phase 0 of the action potential (Vmax). Since levocetirizine did not affect the maximum upstroke velocity indicates that the sodium channel was not affected. In anesthetized dogs, the sinus node was crushed in addition to the administration of propranolol produced a long Qt syndrome. Doses of 0.8, 1.6 and 3.2 mg/kg of levocetirizine infused intravenously over 1 hr did not produce a proarrythmic liability. In anesthetized rats, levocetirizine at intravenous doses of 14.8 and 25.9 mg/kg produced a transient decrease in diastolic pressure and heart rate; this was followed by partial recovery of the blood pressure and full recovery from the bradycardia. In anesthetized dogs, cumulative intravenous doses starting at 4.6 mg/kg and ending at 138.2 mg/kg produced bradycardia at 4.6 mg/kg; at doses $\geq$ 46.2 mg/kg, there were transient tachycardia and disturbance of conduction and repolarization. One animal died at 46.2 mg/kg, and the remaining 3 animals died at 138.2 mg/kg. Levocetirizine at cumulative intravenous doses of 1, 3.2 and 10 mg/kg to anesthetized dogs did not affect the systolic, diastolic, mean blood pressure, heart rate, left ventricular systolic pressure, left ventricular dp/dt maximum, cardiac output, ECG, femoral flow, femoral resistance, respiratory rate, minute volume, and blood gases. In a gastrointestinal study in rats, levocetirizine at oral doses of 25, 50 and 100 mg/kg did not affect gastrointestinal transit time.
Studies with the metabolite, (P026) in rabbits, did not change the EEG by the oral and by the intravenous routes did not affect the autonomic, central nervous and respiratory systems.

2.6.2.2 Primary pharmacodynamics

Drug activity related to proposed indication:

The following tables excerpted from the submission describe the antihistaminic and related pharmacological activities of levocetirizine, cetirizine and S-cetirizine.

In most studies levocetirizine was more potent than cetirizine and S-cetirizine.
Note: In the *in vitro* inhibition of the [^{3}H] mepyramine binding to human H_1 receptors expressed in CHO cells assay [RRLE95M1801], the average dissociation t1/2 ± S.D. for

levocetirizine was 115 ± 38 min and 95 ± 33 min for cetirizine which were not statistically different.

Table 2:2 Studies Investigating the Activity of Levocetirizine

Model	Species	Result
Inhibition of [^{3}H]-mepyramine binding in mouse cerebral cortex [RRLE95A0510]	*In vitro*	IC_{50} (pIC_{50}): Levocetirizine: 12 nM (7.9) Cetirizine: 27 nM (7.6) ucb 28557: 310 nM (6.5)
Inhibition of [^{3}H]-mepyramine binding to human H_1 histamine receptors expressed in CHO cells [RRLE95M1801]	*In vitro*	Binding properties (Ki, pKi, dissociation $t_{1/2}$): Levocetirizine: 2-3 nM, 8.5 and 115-142 min Cetirizine: 6 nM, 8.2 and 95 min ucb 28557: 80 nM, 7.1 and 6-7 min
Affinity and selectivity for human H_1 histamine receptors [RRLE96A1901]	*In vitro*	Binding properties (Ki, pKi,): Levocetirizine: 2 nM; 8.6 Cetirizine: 6 nM; 8.2 ucb 28557: 80 nM; 7.1 Levocetirizine binds to H_1 receptors with > 500 fold higher affinity than to 13 other receptors
Binding to cloned human H_1 histamine receptors and to cloned human muscarinic receptor subtypes [ADPE03B1704]	*In vitro*	Binding properties (Ki, pKi,): Levocetirizine: 2 nM; 8.6 Cetirizine: 6 nM; 8.2 Levocetirizine binds to H_1 receptors with > 20,000 fold higher affinity than to the 5 subtypes of muscarinic receptors and has no effect on M2 mediated inhibition of inotropic effect in paced atria in the guinea pig: comparison with desloratadine
Inhibition of [^{3}H]-levocetirizine binding to human H_1 histamine receptors expressed in CHO cells [ADPE02E1404]	*In vitro*	Binding properties (Kd, pKi, dissociation $t_{1/2}$): Levocetirizine: 3 nM, 8.4 and 134 min
Contribution of Lys (191) and Thr (194) to binding to human H1 histamine receptors [ADPE02A3102]	*In vitro*	Binding properties (Ki, pKi, dissociation $t_{1/2}$): Levocetirizine: 3 nM, 8.5 and 142 min Cetirizine: 6 nM, 8.2 ucb 28557: 100 nM, 7.0 and 6 min Levocetirizine binds competitively with histamine to H_1 receptors; its high affinity and slow dissociation kinetics are due to an interaction with Lys^{191} of the receptor and its stereoselectivity is in part due to Thr^{194}
H_1 histamine receptor affinity and NF-κB activity in transfected COS-7 cells [ADPE02B2701]	*In vitro*	Ki, pKi and NF-κB reporter gene inhibition: Levocetirizine: 16 nM, 7.8 and 59% ucb 28557: 160 nM, 6.8 and 62%

Model	*Species*	Result
Antagonism of histamine-induced contraction of guinea pig trachea after 5 min preincubation with compounds [RRLE92E2004]	*In vitro*	IC_{50}, pA_2: Levocetirizine: 31 nM, nd Cetirizine: 62 nM, nd ucb 28557: nd, 7.4
Antagonism of histamine-induced contraction of guinea pig ileum after 5 min preincubation with compounds [RRLE92E2003]	*In vitro*	IC_{50}: Levocetirizine: 2 µM Cetirizine: 2 µM ucb 28557: 5 µM
Antagonism of histamine-induced contraction of isolated Guinea pig ileum and trachea [ADPE03F0305]	*in vitro*	pA_2 Ileum / Trachea Levocetirizine 8.3 / 7.9 Cetirizine 8.0 / 7.3 ucb 28557 7.1 / 6.4 Antagonism by levocetirizine is mixed (surmountable and insurmountable) due to its slow dissociation kinetics from the receptors and is dependent on the receptor reserve in the tissue.
Inhibition of histamine-induced spasms following single iv dosing at 0.32 µmol/kg (0.15 mg/kg) [RRLE95G1801]	Anesthetized guinea pig	Time to and extent of maximal spasm inhibition: Levocetirizine: from 42 min (98%) Cetirizine: from 42 min (65%) ucb 28557: from 17 min (45%)
Inhibition of histamine-induced wheal size following single po dosing at 0.005-0.5 mg/kg [RRLE95A0509]	NMRI mouse	ED_{50}: Levocetirizine: 0.03 mg/kg [0.06 µmol/kg] Cetirizine: 0.09 mg/kg [0.20 µmol/kg] ucb 28557: 0.06 mg/kg [0.13 µmol/kg]
Inhibition of histamine-induced wheal size following single po dosing at 0.005-0.5 mg/kg [RRLE95E2901]	NMRI mouse	ED_{50} (comparing inhibition after 1 vs 2 µg histamine): Levocetirizine: 0.017 and 0.018 mg/kg Cetirizine: 0.073 and 0.078 mg/kg ucb 28557: 0.039 and 0.148 mg/kg
Inhibition of histamine-induced wheal size following single po dosing at 0.005-0.5 mg/kg [RRLE95A0502]	SD rat	ED_{50}: Levocetirizine: 0.9 mg/kg [2 µmol/kg] Cetirizine: 2 mg/kg [3 µmol/kg] ucb 28557: 5 mg/kg [11 µmol/kg]
Inhibition of histamine-induced wheal size following single po dosing at 0.32 µmol/kg (0.15 mg/kg) in a cross-over design (2 weeks between treatments) [RRLE95A0504]	Beagle dog	Time of and maximum wheal inhibition: Levocetirizine: 3.5-6.5 h and 58% Cetirizine: 3.5-6.5 h and 48% ucb 28557: inactive (14% inhibition)

nd : not determined

Model	Species	Result
Inhibition of histamine-induced wheal size following single po dosing at 0.32 µmol/kg (levocetirizine) or 1 and 3.2 µmol/kg (ucb 28557) in a cross-over design (2 weeks between treatments [RRLE95A1202]	Beagle dog	Time of and maximum wheal inhibition: Part A: Levocetirizine: 2 h and 79% Part A: ucb 28557 at 1 µmol/kg: 2.7 h and 49% Part B: Levocetirizine: 0.7 h and 73% Part B: ucb 28557 at 3.2 µmol/kg: 2.7 h and 52%
Antihistaminic activities and general pharmacology of ucb P026 (metabolite) [RXLE94E2705]	*in vitro*, *in vivo* rat, Guinea pig, dog and rabbit	ucb P026 inhibits histamine induced ileum contraction *in vitro* with an IC_{50} of 18µM and show inhibition of histamine induced airway constriction *in vivo* with an ID_{50} of 3 mg/kg.

2.6.2.3 Secondary pharmacodynamics

Activity and selectivity profile of cetirizine, levocetirizine and S-cetirizine for human H_1 receptors, No. RRLE96A1901.

Levocetirizine, cetirizine and S-cetirizine were tested at 10 umol/l to determine their ability along with different pharmacological classes that also bind to G-protein coupled receptors. The results in the following table excerpted from the submission show that levocetirizine, cetirizine and S-cetirizine almost completely (89-100%) inhibited the H_1 radioligand. For 12 non-H_1 radioligand receptors, at 10 umol/l, the inhibition was weak ranging from -2% to 82% for levocetirizine, -2% to75% for cetirizine and -2% to 43% for S-cetirizine. This indicates that levocetirizine, cetirizine and S-cetirizine in this limited study have a selective affinity for the H_1 receptors.

TABLE 2 : Binding profiles of ucb 28556, ucb 28557 and cetirizine

RECEPTOR	% INHIBITION OF RADIOLIGAND SPECIFIC BINDING			QUALITY CONTROL		REFERENCE	
	ucb 28556 (10 µmol/l)	ucb 28557 (10 µmol/l)	Cetirizine (10 µmol/l)	Substances ([nmol/l])	% Inhibition of radioligand specific binding	Substances	pKi (-logM)
A_1 Adenosine	11 ± 5 (n=3)	8 ± 4 (n=3)	0 ± 6 (n=3)	2-CADO (100)	63 ± 6 (n=48)	CPDMX	7.3 ± 0.1 (n=3)
α_1-Adrenergic	57 ± 5 (n=3)	9 ± 6 (n=3)	44 ± 8 (n=3)	WB4101 (3)	47 ± 9 (n=46)	WB4101	9.1 ± 0.1 (n=3)
α_2C2-Adrenergic	44 (n=1)	1 (n=1)	35 (n=1)	Mivazerol (30)	43 ± 9 (n=32)	RX821002	8.1 ± 0.1 (n=3)
α_2C4-Adrenergic	82 ± 1 (n=3)	43 ± 2 (n=3)	75 ± 1 (n=3)	Mivazerol (10)	50 ± 9 (n=48)	RX821002	8.6 ± 0.3 (n=3)
α_2C10-Adrenergic	29 ± 2 (n=3)	8 ± 3 (n=3)	22 ± 2 (n=3)	Mivazerol (30)	33 ± 4 (n=33)	RX821002	8.7 ± 0.2 (n=3)
ß-Adrenergic	4 ± 2 (n=3)	3 ± 2 (n=3)	1 ± 8 (n=3)	Isoproterenol (100)	41 ± 4 (n=46)	Propranolol	8.8 ± 0.0 (n=2)
D_2 Dopamine	5 ± 6 (n=3)	-2 ± 1 (n=3)	2 ± 2 (n=3)	Chlorpromazine (10)	71 ± 8 (n=47)	Chlorpromazine	8.9 ± 0.1 (n=2)
H_1 Histamine	100 ± 1 (n=3)	98 ± 1 (n=3)	100 ± 1 (n=3)	Cetirizine (10)	43 ± 5 (n=35)	Cetirizine	8.3 ± 0.1 (n=4)
H_2 Histamine	22 ± 13 (n=3)	15 ± 14 (n=3)	15 ± 11 (n=3)	Ranitidine (300)	45 ± 8 (n=33)	Ranitidine	6.7 ± 0.1 (n=3)
H_3 Histamine	3 ± 1 (n=3)	6 ± 4 (n=3)	-2 ± 3 (n=3)	Thioperamide (30)	64 ± 7 (n=43)	Thioperamide	7.9 ± 0.1 (n=3)
Muscarinic	2 ± 1 (n=3)	4 ± 2 (n=3)	6 ± 6 (n=3)	Pirenzepine (100)	70 ± 7 (n=48)	Atropine	8.7 ± 0.1 (n=2)
5-HT_{1A}	-2 ± 4 (n=3)	-2 ± 1 (n=3)	0 ± 3 (n=3)	Mivazerol (1000)	76 ± 8 (n=45)	Buspirone	8.2 ± 0.1 (n=4)
5-HT_2	33 ± 1 (n=3)	7 ± 1 (n=3)	32 ± 10 (n=3)	Chlorpromazine (10)	66 ± 9 (n=45)	Ritanserine	8.5 ± 0.2 (n=3)

2.6.2.4 Safety pharmacology

Neurological effects:

Effect of levocetirizine on the general behavior and antihistaminic activity in mice, No. LE88B242.

Groups of 3 male mice received levocetirizine orally or intraperitoneally. The behavior changes are summarized in the following table. The animals were observed at 5, 15, 30, 60 and 120 min and at 24 hrs following administration.

Dose, mg/kg, Route	Results
i.p.	
14	No behavior changes.
46	Piloerection; decreased muscle tone and motor activity.
92	Piloerection; greater decrease in muscle tone and motor activity; tremors.
138	Piloerection; greater decrease in muscle tone and motor activity; tremors; lack of motor activity; decreased pinna reflex; cyanosis and death in all 3 mice within 24 hours.
Oral	
46	No behavior changes.
138	Slight decrease in body tone; piloerection; reddening of the skin.
462	Piloerection; decrease in muscle tone and motor activity; tremors; lack of motor activity; reddening of the skin; hyperpnea.
1384	Piloerection; decrease in muscle tone and motor activity; tremors; lack of motor activity; reddening of the skin; hyperpnea; hypothermia and death. Death occurred within 24 hrs.

Effect of oral and intraperitoneal levocetirizine on the general behavior in mice, No. RRLE92E0508.

Groups of 3 male NMRI mice (18-22 g) received 1.3, 4.6, 13.8, 46.1, 92.3 and 138 mg/kg, intraperitoneally or 46.1, 138.5 and 461.8 mg/kg, orally of levocetirizine. They were observed at 5, 15, 30 and 60 min post treatment. Control animals received the vehicle. The results are shown in the following table excerpted from the report. Some evidence of central nervous system depression was seen at intraperitoneal doses as low as 4.6 mg/kg, which increased until tremors and lethality occurred at 138.5 mg/kg. By the oral route, central nervous system depression occurred at 138.5 mg/kg; 461.8 mg/kg was lethal.

Table I: Effects of ucb 28556 on the general behaviour of the mouse after intraperitoneal or per os administration. The observations below indicate the minimal dosage at which these behavioural modifications were noted.

Doses mg/kg	Doses mmol/kg	Observed effects after intraperitoneal administration	Observed effects after per os administration
1.3	0.003	No observed effects	Not tested
4.6	0.01	↓ body tone	Not tested
13.8	0.03	↓ spontaneous activity, piloerection	Not tested
46.1	0.10	Hypoactivity, onset of sedation (↓ vigilance, exploration and reactivity), ↑ touch escape activity, ↓ grooming, contorsions	No observed effects
92.3	0.20	Tremors, hypotonicity (↓ limb tone, body resistance and abdominal tone)	Not tested
138.5	0.30	Central nervous system excitation (tremors), lethality	↓ spontaneous activity, ↓ grooming, ↓ body tone, piloerection, flush
461.8	1.0		Hypoactivity, onset of sedation (↓ reactivity and touch escape activity), lethality

↓ decrease; ↑ increase with respect to vehicle treated control mice.

Effect of levocetirizine on hexobarbital induced sleeping time in mice, No. RRLE95A0505.

Groups of 10 male NMRI mice (26-32 g) received the vehicle, 25.9, 46.2 and 83.1 mg/kg intraperitoneally of levocetirizine, 60 minutes after the intraperitoneal administration of 30 mg/kg of hexobarbital. The time it took from the onset to the recovery of the righting reflex to recover was determined. Levocetirizine increased the duration of the loss of righting reflex only at 83.1 mg/kg (C: 2.8 min; T, 18.1 min).

Effect of cetirizine and levocetirizine on the general locomotor activity of rats, No. TA0467.

Groups of 5 male SD (Crl:CD BR) rats (160-210 g) received 25, 50 and 100 mg/kg, orally of levocetirizine. Control animals received the vehicle purified water orally (10 ml/kg). Locomotor activity was measured by a Photobeam Activity System. The positive control was 5 mg/kg subcutaneously of amphetamine. Thirty minutes following oral administration, locomotor activity was measured at 15 minute intervals over a 2 hour period. Levocetirizine produced no effect on the locomotor activity.

Effect of levocetirizine and cetirizine on general activity and behavior (Irwin Test), No. RRLE99A1104

Groups of 6 rats received levocetirizine (25, 50 and 100 mg/kg, orally). Another group received 15 mg/kg subcutaneously of chlorpromazine as the positive control. Assessment of the general behavior was determined by the Irwin test which consisted of 50 parameters. Changes from predose to 1, 2, 4 and 6 hr post dose were determined. The only effect noted was a dose related increase in positional passivity. The reference produced signs of central nervous depression in 10 of the 50 parameters, e.g., decreased transfer arousal, body and abdominal tone, spatial locomotion and hypotonic gait.

Effect of cetirizine and levocetirizine on pentobarbital sleeping time in rats and the general locomotor activity of rats, No. RRLE99A1105.

Groups of 6 male SD (Crl:CD BR) rats (158-168 g) received 25, 50 and 100 mg/kg, orally of levocetirizine. Control animals received the vehicle (purified water) orally (10 ml/kg). The positive control was 20 mg/kg intraperitoneally of bemegride. Sixty minutes following oral administration, the animals received 50 mg/kg of intravenous pentobarbital. The time it took from the onset to the recovery of the righting reflex to recover was determined. Levocetirizine had no effect on the duration of the pentobarbital- induced righting reflex in rats.

Cardiovascular effects:

Effect of levocetirizine and cetirizine on the Xenopus laveis oocytes hERG K^+ assay, No. RRLE99B1801.

Both levocetirizine and cetirizine were inactive at 30 uM in inhibiting the K^+ channel in the Xenopus laveis oocytes hERG K+ assay.

Effect of Levocetirizine, cetirizine and S-cetirizine on the guinea pig K^+ current effects using ventricular myocytes assay, No. ADPE98G0201.

At 0.1 mM, blockage of the K+ current was 55% for levocetirizine, 51 % for cetirizine and 35% for S-cetirizine indicating that levocetirizine and cetirizine were comparable and more active than S-cetirizine.

Effect of cetirizine, levocetirizine and S-cetirizine on the action potentials of canine cardiac Purkinje fibers, No. TB0392.

The effect of levocetirizine on the repolarization process was determined in the Purkinje fibers of 7 Beagle dog's hearts. Cumulative concentrations of 0.3, 3, 30 and 300 uM, 15 min apart were tested. Then, each concentration was allowed to equilibrate for 15 minutes before being paced at cell lengths of 1000, 2000, 4000 and 8000 ms. Measurements made of the action potential characteristics were: maximal potential characteristics (MDP), action potential amplitude (APA), maximum upstroke velocity at of phase 0 of the action potential (Vmax), and the action potential duration at 30% (APD30), 50% (APD50), 70% (APD70) and 90% (APD90). The results in the following table excerpted from the submission show that levocetirizine at 30 and 300 uM significantly prolonged the APD50, APD70 and APD90 with no effect on the ADP30, MDP, APA and Vmax.

	Control	ucb 28556			
		0.3 μM	3 μM	30 μM	300 μM[3]
MDP (mV)					
1000 ms	-90.7 ± 1.1	-90.4 ± 1.5	-91.1 ± 0.9	-90.9 ± 1.0	-89.9 ± 0.8
2000 ms	-89.9 ± 1.1	-90.1 ± 1.3	-90.3 ± 0.8	-90.6 ± 1.0	-88.6 ± 1.1
4000 ms	-89.0 ± 1.2	-88.6 ± 1.4	-89.9 ± 1.1	-89.7 ± 0.8	-88.2 ± 0.8
8000 ms	-88.7 ± 1.5	-89.7 ± 1.1	-89.4 ± 1.3	-89.0 ± 1.0	-88.2 ± 0.6
APA (mV)					
1000 ms	124.0 ± 1.6	121.6 ± 1.6	122.1 ± 1.4	122.6 ± 1.5	121.3 ± 1.3
2000 ms	122.4 ± 1.7	121.3 ± 1.9	120.9 ± 1.4	122.0 ± 1.6	119.9 ± 1.4
4000 ms	121.9 ± 1.6	119.0 ± 1.4	121.0 ± 1.8	120.0 ± 1.4	118.5 ± 1.1 *
8000 ms	120.1 ± 1.6	119.2 ± 1.2	120.0 ± 2.1	119.0 ± 1.6	120.4 ± 2.3
V_{max} (V/s)					
1000 ms	530 ± 70	523 ± 69	533 ± 79	537 ± 85	530 ± 75
2000 ms	523 ± 63	517 ± 67	527 ± 79	530 ± 81	523 ± 77
4000 ms	503 ± 62	503 ± 67	513 ± 77	513 ± 82	550 ± 96
8000 ms	497 ± 68	500 ± 70	503 ± 77	500 ± 76	510 ± 84
APD_{30} (ms)					
1000 ms	86 ± 11	93 ± 9	95 ± 14	90 ± 12	70 ± 11 *
2000 ms	101 ± 18	102 ± 15	106 ± 19	102 ± 17	85 ± 12
4000 ms	102 ± 17	108 ± 19	111 ± 19	112 ± 18	88 ± 17
8000 ms	109 ± 18	107 ± 21	113 ± 25	118 ± 24	96 ± 14
APD_{50} (ms)					
1000 ms	200 ± 15	207 ± 15	214 ± 17	224 ± 16 *	226 ± 15 *
2000 ms	238 ± 21	241 ± 17	249 ± 20	281 ± 21 *	301 ± 24 *
4000 ms	257 ± 23	262 ± 21	284 ± 22	327 ± 29 *	357 ± 41 *
8000 ms	270 ± 26	266 ± 27	279 ± 36	326 ± 40	402 ± 56
APD_{70} (ms)					
1000 ms	257 ± 24	260 ± 24	274 ± 25	309 ± 31	378 ± 42 *
2000 ms	282 ± 21	291 ± 17	301 ± 20	343 ± 20 *	426 ± 24 *
4000 ms	311 ± 24	322 ± 23	341 ± 24	394 ± 29 *	537 ± 44 *
8000 ms	324 ± 27	321 ± 27	338 ± 35	393 ± 38	613 ± 84 *
APD_{90} (ms)					
1000 ms	276 ± 16	281 ± 15	291 ± 15	309 ± 13 *	368 ± 14 *
2000 ms	324 ± 21	330 ± 19	340 ± 21	386 ± 19 *	515 ± 29 *
4000 ms	353 ± 25	373 ± 28	385 ± 25	444 ± 29 *	663 ± 56 *
8000 ms	370 ± 28	364 ± 25	377 ± 33	439 ± 36	738 ± 92 *

Abbreviations are: MDP, maximum diastolic potential; APA, action potential amplitude; V_{max}, maximum upstroke velocity of phase 0; APD_{30}, APD_{50}, APD_{70} and APD_{90}, action potential duration at 30, 50, 70 and 90% of full repolarisation, respectively. * $p<0.05$ vs control.

Hemodynamic effect of levocetirizine in anesthetized Sprague Daley rats, No. RRLE95A0507.

Groups of 6 male anesthetized male rats (250-300 g) were administered intravenously by the femoral artery, 4.6, 14.8 and 25.9 mg/kg. Heart rate and diastolic pressure were measured over 60 min following drug administration. Within 6 min, there at 14.8 was a transient decrease (-55%) in blood pressure and heart rate (-29%) followed by a 17% increase in blood pressure and 8% increase in heart rate at and at 25.9 mg/kg there was a transient decrease (-58%) in blood pressure and heart rate (-36%) followed by a 18% increase in blood pressure and 18% decrease in heart rate.

Acute circulatory tolerance of cumulative intravenous doses of levocetirizine in anesthetized dogs, No. RRLE93H0901.

Four anesthetized Beagle dogs received cumulative increasing half log intravenous doses at 20 min intervals from 4.62 ug/kg to 138.2 mg/kg of levocetirizine. Blood pressure and heart rate were continually monitored. Transient decrease in blood pressure occurred at doses up to 13.9 mg/kg. At 4.6 mg/kg, bradycardia was observed. From doses ≥46.2 mg/kg, there were transient tachycardia, disturbances of conduction and repolarization (ST-segment depression and ventricular fibrillation). One animal died at 46.2 mg/kg and the remaining three animals died at 138.5 mg/kg. In this study, cardiac toxicity was probably the cause of death in the anesthetized dogs.

Effect of levocetirizine and cetirizine on cardiac rhythm in a model of acquired long QT syndrome in halothane anesthetized dogs, No. RRLE96K0402.

Groups of 7-9 halothane anesthetized Beagle dogs received 3 intravenous doses infused over 1 hr at a constant rate of 0.8, 1.6 and 3.2 mg/kg/hr. The control animals received the vehicle (saline) at the same rate. Bradycardia was induced by destroying the sinus node with a clamp along with the intravenous administration of propranolol (0.6 mg/kg in 10 min). Both levocetirizine and cetirizine produced no effect on the femoral blood pressure, EKG and mean arterial pressure. Similar findings were seen with cetirizine.

Effect of intravenous levocetirizine on the cardiovascular and respiratory systems in anesthetized dogs, No. RRLE96K0402.

A group of 4 anesthetized dogs received cumulative intravenous doses of 1, 3.2, and 10 mg/kg infused over a 5 min period. The following parameters were measured: systolic, diastolic, mean pressure, heart rate, left ventricular systolic pressure, left ventricular dp/dt maximum, cardiac output, EGG, femoral flow, femoral resistance and respiratory parameters. Levocetirizine produced no effect on the cardiovascular system up to 10 mg/kg in anesthetized dogs.

Pulmonary effects:

Effect of intravenous levocetirizine on the cardiovascular and respiratory systems in anesthetized dogs, No. RRLE96K0402.

A group of 4 anesthetized dogs received cumulative intravenous doses of 1, 3.2, and 10 mg/kg infused over a 5 min period of levocetirizine in anesthetized dogs. There was no effect on the respiratory rate, minute volume, and blood gases.

Renal effects:

No studies were submitted.

Gastrointestinal effects:

Effect of cetirizine and levocetirizine on gastrointestinal transit in rats, No. RRLE99A1107.

Groups of 6 male rats received oral doses of 0 (10 ml/kg, water) 25, 50 and 100 mg/kg of levocetirizine or 20 mg/kg subcutaneously of morphine (positive control). A charcoal meal was administered orally 60 min following oral administration of levocetirizine or 30 min following subcutaneous administration of morphine. Ten minutes following administration of the meal, the animals were killed, and the distance over the gastrointestinal tract the meal traveled was determined. Levocetirizine did not affect the transit time while morphine decreased the transit time by 85%.

Abuse liability: NA

Other: None.

2.6.2.6 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY: NA.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

In Beagle dogs, radioactive levocetirizine was given single or 8 daily doses of 1 mg/kg orally. Cmax, tmax, whole blood radioactivity, plasma radioactivity levels, distribution (muscle, liver and bile) and t1/2 were similar upon single and multidose administration. Following the administration of 1 mg/kg, intravenously, plasma and urinary pharmacokinetics of levocetirizine was compared with S-cetirizine in dogs. Plasma (t1/2, AUC, MRT, Vd_{ss} and CL) urinary (renal clearance, t1/2, and excretion expressed as % of the dose were higher than S-cetirizine. In characterizing its transport, a study conducted in Caco-cells indicated that levocetirizine was not affected by the P-glycoprotein but passed through cells by diffusion. Single oral doses of 2 and 25 mg/kg in male and non-pregnant and pregnant rats show that pregnant rats at 2 mg/kg had higher blood and plasma radioactivity levels than the non-pregnant rats which had levels similar to males. However, at the higher dose, 25 mg/kg, the blood and plasma radioactivity levels in non-pregnant and pregnant rats were similar but higher than males indicating that in rats, levels in the blood and plasma in non-pregnant rats were dependent on the dose.

In rats, distribution studies were determined by autoradiography conducted with a single oral dose of 2 mg/kg of radioactive levocetirizine in male, and non-pregnant and pregnant rats. The highest concentrations of radioactivity occurring 2 hr post dose were in the gastrointestinal tract and in the liver, kidney and pancreas of all rats. The pregnant rats showed higher levels in the liver and kidney than the non-pregnant and male rats. Radioactivity in the, placenta, fetus, brain were less than the background (1.6 ug eq/g tissue) or were not detectable in other tissues.

In the single and multidose study (8 days) in dogs receiving 1 mg/kg, orally, distribution of radioactivity was determined in 38 tissues. The highest concentrations occurred at 2 hr post dose in decreasing order were the bile, liver and kidneys. The brain shows levels that were 12% of plasma level and 19% of the blood level. However, the ratio of tissue radioactivity to plasma unbound levocetirizine levels, the brain stem, cerebrum and cerebellum brain was more than 2 at the 24 hours post dose.
In vitro metabolism studies were conducted with rat liver fractions. At 5uM of [^{14}C] levocetirizine, 87% of the doses were transformed, and 8 metabolites were detected when hepatocytes were used. With NADPH fortified liver microsomes from untreated male rats were used, 4% of levocetirizine was metabolized with only 1 metabolite being detected. Additional studies indicate that conjugation was involved in the metabolism. Metabolism was increased to 10% when microsomes from dexamethasone-treated male rats were used indicating that P-450 enzymes were involved in the metabolism.
In rats, the main metabolites were M1, M2, F11 and F12. Females metabolize levocetirizine to a greater degree than males. In dogs, the major metabolites being M7+M8 (16-23% of the dose) and M10 (8-13% of the dose) along with unchanged levocetirizine. In protein binding studies in dogs, binding was 89% in vitro and 91% ex vivo.
Excretion in rats was fecal and urinary. At 2 and 25 mg/kg in non- pregnant and pregnant females 46 % of the dose in the urine was unchanged levocetirizine in the 0-24 hr sample. This represented 90 % of the total radioactivity in the urine. In males, 1% - 2% of the dose was excreted in the urine as unchanged levocetirizine in the 0-24 hr sample. In another study with non-pregnant, pregnant and male rats receiving 2 or 25 mg/kg, orally, urinary excretion at the 2 mg/kg in both females was 40% of the 2 mg/kg and 63% of the 25 mg/kg dose indicating that urinary excretion increased with the dose. Males on the other hand excreted 82 % of the dose in the feces at both doses. This difference in excretion was confirmed in the balance of excretion study using the same doses. In dogs receiving a single or multi oral dose of 1 mg/kg for 8 days, excretion was predominantly fecal (57-63%) followed by urinary excretion (17-35%).

2.6.4.2 Methods of Analysis

Plasma levels were determined by Gas Chromatography equipped with a NPFID detector. The limit of detection was 0.02ug/ml.

2.6.4.3 Absorption

Comparative pharmacokinetics in Beagle dogs, No. LE88B021

The study was conducted in Beagle dogs; three males and 3 females received 1 mg/kg intravenously of levocetirizine (UCB28556) or S-cetirizine (UCB28557). Comparison was made of the plasma (0-48 hr) and urinary (0-48 hr) pharmacokinetics. The results are summarized in the following tables excerpted from the submission. The plasma (terminal rate constant, terminal t1/2, AUC, MRT, and CL) and urinary (excretion t1/2) pharmacokinetics were similar between the two enantiomers; S-cetirizine was different in

showing a higher volume of distribution, a higher total excretion fraction and a higher renal clearance.

Plasma Pharmacokinetics

PARAMETERS	UNIT	Levocetirizine ucb 28556		S-cetirizine ucb 28557	
Terminal rate constant (β)	1/h	0.08524	(0.00792)	0.07200	(0.00829)
Terminal half-life (t 1/2)	h	8.20	(0.75)	9.74	(1.12)
Area under curve	µg.h/ml	36.4	(8.8)	26.7	(4.0)
Volume of distribution Vd_{SS}	l/kg	0.32	(0.07)	0.51	(0.07)
Clearance (D/AUC)	ml/min/kg	0.487	(0.134)	0.638	(0.103)
Mean Residence Time (MRT)	h	11.15	(1.28)	13.30	(1.45)

Urinary Pharmacokinetics

PARAMETERS	UNIT	ucb 28556		ucb 28557	
Excretion half-life (t 1/2)	h	7.80	(1.76)	8.25	(1.68)
Total excreted fraction	% dose	25.6	(2.1)	38.1	(3.4)
Renal clearance (Au/AUC)	ml/min/kg	0.123	(0.029)	0.243	(0.044)

Metabolism and pharmacokinetics [^{14} C] levocetirizine in rats following a single oral administration by gavage, No. RRLE95H0901

Groups of 10 male, 10 female and 8 pregnant rats received by gavage, a single dose of 2 and 25 mg/kg of radioactive levocetirizine. Pregnant rats received levocetirizine on day 14 of gestation. Radioactivity was measured in blood and plasma (0.5, 1, 2, 4, 8, 12, 24, 48, 96, and 168 hr in male and non-pregnant females and up to 48 hr in pregnant rats Blood and plasma levels are presented in the following table excerpted from the submission.

	2 mg /kg			25 mg /kg		
Parameter	M	F	Preg.	M	F	Preg.
Whole blood						
Radioactivity t_{max} (h)	0.5	0.5	1	2	0.5	1
Radioactivity C_{max} (µg eq/ml)	0.67	0.33	1.03	9.34	18.53	15.76
Plasma						
Radioactivity t_{max} (h)	0.5	0.5	1	2	0.5	1
Radioactivity C_{max} (µg eq/ml)	1.0	0.46	1.38	14.60	22.93	21.18
ucb 28556 t_{max} (h)	0.5	0.5	2	2	0.5	1
ucb 28556 C_{max} (µg/ml)	1.14	0.44	1.18	13.55	23.95	23.68

In blood and plasma, pregnant rats at 2 mg/kg, orally, of levocetirizine show higher Cmaxs based on radioactivity and levocetirizine (blood and plasma) than non-pregnant females and males; however, at 25 mg/kg, orally, both non-pregnant and pregnant females show higher Cmaxs (blood and plasma) than males.

Absorption distribution, metabolism and elimination of [14C] levocetirizine after oral administration to Beagle dogs, No. RRLE99L1301

The study was conducted in Beagle dogs; two males and 2 females received single or 8 daily oral radioactive doses of 1 mg/kg. Radioactivity was determined in whole blood and plasma up to 48 hr following the administration of the single and 8 daily doses. The pharmacokinetics is shown in the following table excerpted from the submission.

pharmacokinetic parameters are summarized in the following table :

Whole-blood radioactivity

	Single*	Repeated§
C_{max} (µg eq/ml)	1.75 ± 0.31	2.23 ± 0.37
t_{max} (h)	1.7 ± 1.1	2.5 ± 2.5

Plasma radioactivity

	Single*	Repeated§
C_{max} (µg eq/ml)	2.56 ± 0.69	2.99 ± 0.64
t_{max} (h)	2.1 ± 1.2	2.8 ± 2.2

Plasma ucb 28556

	Single#	Repeated§
C_{max} (µg/ml)	2.53 ± 0.91	2.96 ± 0.66
t_{max} (h)	3.3 ± 1.5	3.0 ± 2.0
AUC (µg.h/ml)	35.2 ± 14.3	
CL/f (ml/min/kg)	0.54 ± 0.23	
Vz/f (l/kg)	0.34 ± 0.14	
$t_{1/2}$ (h)	7.84 ± 3.64	8.87 ± 1.02
λ_z (h^{-1})	0.107 ± 0.055	
AUC_{ss}(µg.h/ml)		37.6 ± 9.7
C_{av} (µg/ml)		1.57 ± 8.4
% PTF		166.4 ± 27.2
% swing		477.2 ± 122.2
CL_{ss}/F (ml/min/kg)		0.464 ± 0.124

* : including Day 1 of repeated administration
\# : on Day 1 of repeated administration
§ : on Day 8 of repeated administration
%PTF : (peak-trough-fluctuation) = $100*(C_{max}-C_{min})/C_{av}$
%swing : (degree of fluctuation) = $100*(C_{max}-C_{min})/C_{min}$

Characterization of the transport through the CACO-2 (HTB-37), No. RLE02A2403

Caco-2 cells belong to an intestinal epithelial cell line derived from human colorectal carcinoma and is used to evaluate intestinal absorption. Levocetirizine was tested at concentrations up to 100 uM to determine whether it affects P-glycoprotein which regulates transportation across cells. At 1-100 uM, transportation of levocetirizine was

not significantly increased in the presence of quinidine, an inhibitor of P-glycoprotein. Since there was no saturation of the P-glycoprotein mechanism, levocetirizine was transported by diffusion across the Caco-2 cells.

2.6.4.4 Distribution

Tissue distribution of total radioactivity in rats following a single oral dose of [14C] levocetirizine, No. RRLE99G1401

The study was conducted in 5 pregnant rats (day 18 of gestation), 5 non-pregnant rats and 5 male rats. The female rats received 2 mg/kg and the male rats 2.1 mg/kg of radioactive levocetirizine. Following oral administration, one pregnant rat was sacrificed at 2, 6, 12 and 48 hr and sectioned; for the non pregnant female and male rats, one rat was sacrificed at 2, 6, 12 and 96 hr and sectioned. Each section was subjected to quantitative whole body autoradiography to measure the distribution of the radioactivity. The highest concentrations of radioactivity were seen at 2 hr in all tissues involved in the absorption, biotransformation and elimination. The highest organ levels were in the gastrointestinal tract, liver, kidney and pancreas. The liver and kidney levels of pregnant rats were greater than those observed in the non-pregnant female and male rats showing a difference in distribution. Levocetirizine crossed the placenta, and the radioactivity found in the fetuses and brain was low, less than the background (1.6 ug eq/g tissue). In other tissues radioactivity was low or not detectable.

Absorption distribution, metabolism and elimination of [14C] levocetirizine after oral administration to Beagle dogs, No. RRLE99L1301

The study was conducted in Beagle dogs; two males and 2 females received single or 8 daily oral radioactive doses of 1 mg/kg. Radioactivity was determined in whole blood and plasma up to 48 hr following the administration of the single and 8 daily doses. The pharmacokinetics is shown in the following table excerpted from the submission.
The distribution of radioactivity in 38 tissues was determined. Levels were similar following single or 8-day administration of 1 mg/kg, orally. Following a single oral dose of 1 mg/kg, the highest concentrations in decreasing order of radioactivity in tissues at 2 hr following administration were bile, liver and kidneys. In the brain, there were low levels relative to plasma and blood levels as shown in the following table. In other tissues, the levels of radioactivity were less than those in the blood.

Tissue	ug eq/g			
	Male, 2h	Female , 6 hr	Male, 24 hr	Female, 48 hr
Plasma	1.778	2.595	0.598	0.100
Blood	1.452	1.687	0.388	0.059
Brain				
Brain stem	0.222	0.266	0.193	0.047
Cerebellum	0.203	0.229	0.129	0.030
Cerebrum	0.177	0.243	0.126	0.136

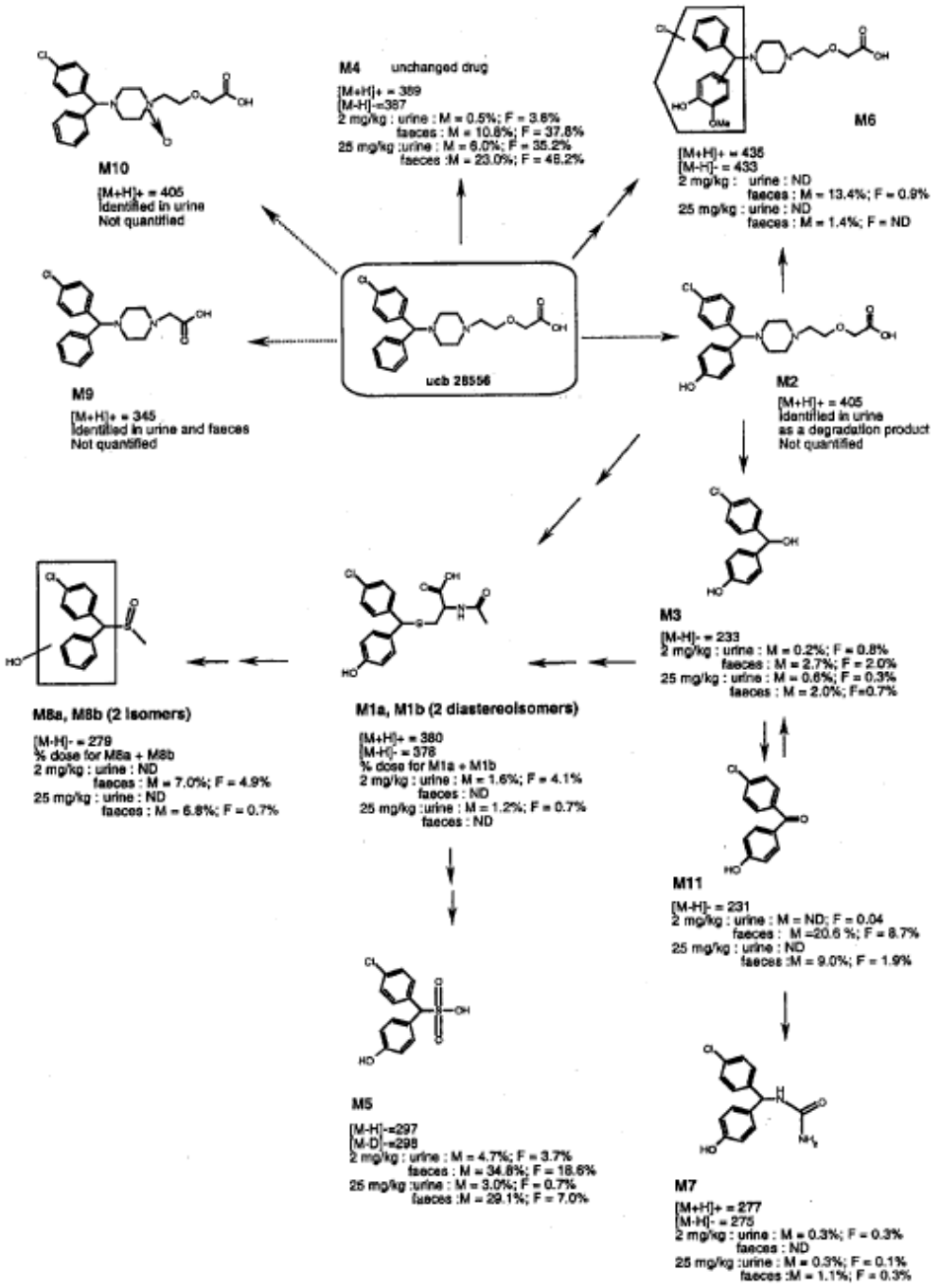
The following table presents the tissue radioactivity/plasma unbound levocetirizine levels ratios at various times following oral administration of 1 mg/kg. Significant levels were still present in the brain at 24 hr relative to the plasma unbound levocetirizine.

Tissue	Tissue Radioactivity/Plasma Unbound Levocetirizine Levels Ratios			
	Male, 2h	**Female , 6 hr**	**Male, 24 hr**	**Female, 48 hr**
Plasma unbound Levocetirizine	0.17 ug eq/ ml	0.31 ug eq/ ml	0.05 ug eq/ ml	Not calculated
Brain				
Brain stem	1.3	0.9	3.6	Not calculated
Cerebellum	1.2	0.7	2.4	Not calculated
Cerebrum	1.1	0.8	2.3	Not calculated

2.6.4.5 Metabolism

Metabolites of [14C] levocetirizine following a single oral dose in rats, No. RRLE00C1503

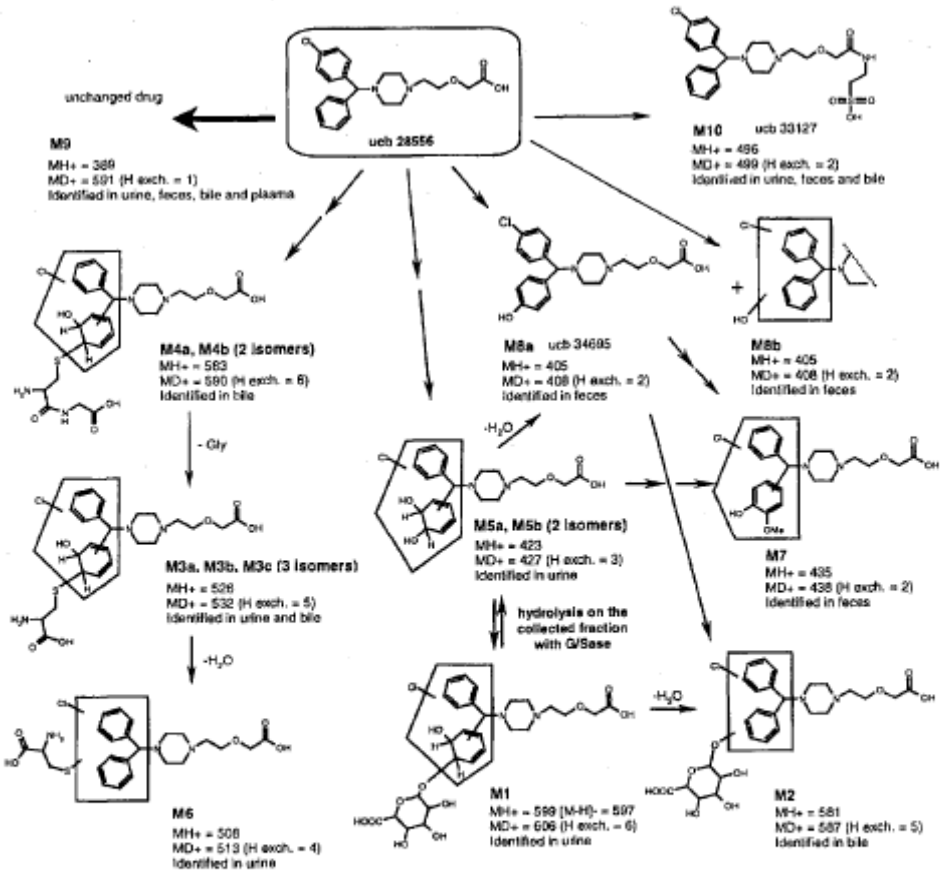
Groups of 2/sex rats received orally 2 or 25 mg/kg of [14C] levocetirizine administered in an isotonic aqueous solution (2 ml/kg). Many metabolites were detected and some were identified structurally as shown in the figure below excerpted from the submission. They were the product of aromatic hydroxylation that ultimately leads to conjugation to form sulfur-containing metabolites as the mercapturates and to a methylated catechol. Other metabolites result from N-oxidation on the nitrogen bearing the ethoxyacetic chain and O-dealkylation.



Scheme 1 - Proposed metabolic pathways of ucb 28556 in the rat. $[M+H]^+$ and $[M-H]^-$ refer to the mass of the pseudomolecular ions as determined by μLC-MS analyses. % of the dose excreted over the 0-48h time interval.

Absorption distribution, metabolism and elimination of [14C] levocetirizine after oral administration to Beagle dogs, No. RRLE99L1301

The study was conducted in Beagle dogs; two males and 2 females received single or 8 daily oral radioactive doses of 1 mg/kg. Radioactivity was determined in whole blood, and plasma up to 48 hr following the administration. In protein binding studies, binding was 89% in vitro and 91% ex vivo. In the metabolism, 14 metabolites plus unchanged levocetirizine were detected. The metabolism of levocetirizine occurred by direct conjugation with taurine followed by aromatic oxidation. The major metabolites were M7+M8 (16-23% of the dose) and M10 (8-13% of the dose). Their structures are shown in the following figure excerpted from the submission.



Scheme 1 Proposed metabolic pathways of ucb 28556 in the dog. MH^+ and MD^+ refer to the mass of the pseudomolecular ions as determined by LC-ESI-MS analysis using respectively water and deuterium oxide as mobile phase component. The number of exchangeable hydrogens (H exch. – usually refers to hydrogens on heteroatoms) was determined from the following equation : H exch. = $MD^+ - MH^+ - 1$.

Preliminary in vitro metabolism using rat liver fractions, No. RRLE99E1001

In vitro studies with were conducted with male rat Hepatocyte and NADPH fortified liver microsomes. Maximum incubation time was 24 hr. At 2.3 ug/ml (5 uM) [^{14} C] levocetirizine, 87% of the dose was biotransformed, and 8 metabolites were detected.

Treatment of the cell extract with B-glucouronidase/sulfatase indicated the presence of a conjugate. When NADPH fortified liver microsomes from untreated male rats were used, 4% of levocetirizine was metabolized with only 1 metabolite being detected. The metabolism was increased to 10% when microsomes from dexamethasone-treated male rats were used. This suggests the P-450 enzymes were involved in the metabolism of levocetirizine.

2.6.4.6 Excretion

Metabolism and pharmacokinetics [^{14} C] levocetirizine in rats following a single oral administration by gavage, No. RRLE95H0901

Groups of 10 male, 10 female and 8 pregnant rats received by gavage, a single dose of 2 and 25 mg/kg of radioactive levocetirizine. Pregnant rats received levocetirizine on day 14 of gestation. Radioactivity was measured in blood and plasma (0.5, 1, 2, 4, 8, 12, 24, 48, 96, and 168 hr in male and non-pregnant females and up to 48 hr in pregnant rats and in 32 tissues following sacrifice. The excretion pattern expressed as % of the dose measured 48 hr after the dosing of pregnant rats and 96 hr after dosing of the male and non-pregnant females are presented in the following table excerpted from the submission.

	2 mg /kg			25 mg /kg		
Parameter	M	F	Preg.	M	F	Preg.
Urine	14.2	40.6	39.9	7.6	58.6	67.0
Cage wash	0.6	1.1	1.2	0.4	1.9	2.3
Faeces	82.9	61.4	63.1	81.5	46.1	13.2
Debris	NS	NS	NS	NS	NS	12.1
GIT	0.97	0.03	1.0	0.08	0.07	0.2
Total	99	103	105	90	107	95

GIT refers to the gastrointestinal tract.

At 2 and 25 mg/kg, 1% and 2% of the dose in males was excreted in the urine as unchanged levocetirizine in the 0-24 hr sample. This represented 10 % and 20% of the total radioactivity in the urine. At 2 and 25 mg/kg in non- pregnant females and pregnant females, 46 % of the dose in the urine was unchanged levocetirizine in the 0-24 hr sample. This represented 90 % of the total radioactivity in the urine. Excretion was mainly fecal in males and urinary in both females. By the excretory pattern, males metabolize levocetirizine more than females.

Retention and balance of excretion of [^{14}C] levocetirizine in rats following a single oral dose, No. RRLE97C0601

Groups of 5 male, 5 female and 5 pregnant rats received by gavage, a single dose of 2 and 25 mg/kg of radioactive levocetirizine. Pregnant rats received levocetirizine on day 14 of gestation. Radioactivity was measured in urine and feces collected up to 168 hr in males and non-pregnant females and up to 96 hr in pregnant animals. At these times, the animals were sacrificed, and radioactivity was measured in blood, gastrointestinal tract (GIT), liver and carcass. Urines were also analyzed for metabolites at 0-8 hr and 0-24 hr.

The results are shown in the following tables excerpted from the submission.

Table IX.
Urinary Excretion of ucb 28556, of ucb 28556 Metabolites and Proportion of Radioactivity Associated to ucb 28556 Following Administration of [^{14}C]-ucb 28556 at Target Doses of 2 and 25 mg/kg.

Sex	Time interval (hours)	ucb 28556 % dose	Metabolites % dose	Proportions of [^{14}C] associated to ucb 28556 %
		p.o. administration at a target dose of 2 mg/kg		
M	0 - 8	0.3 ± 0.6	2.8 ± 2.3	14.3 ± 28.5
	0 - 24	0.7 ± 1.6	9.4 ± 4.4	10.7 ± 23.9
F	0 - 8	11.7 ± 9.7	8.6 ± 3.6	52.7 ± 19.8
	0 - 24	15.2 ± 12.9	15.0 ± 3.4	45.2 ± 20.2
PF	0 - 8	15.2 ± 8.0	11.8 ± 2.8	53.3 ± 20.2
	0 - 24	17.7 ± 9.0	15.9 ± 2.9	49.9 ± 18.9
		p.o. administration at a target dose of 25 mg/kg		
M	0 - 8	3.7 ± 2.5	3.0 ± 1.8	52.2 ± 26.1
	0 - 24	7.1 ± 5.8	7.3 ± 3.3	44.8 ± 29.6
F	0 - 8	36.7 ± 4.8	2.0 ± 0.9	95.0 ± 1.7
	0 - 24	55.9 ± 3.3	3.6 ± 1.7	93.9 ± 3.1
PF	0 - 8	36.6 ± 4.8	2.1 ± 1.0	94.7 ± 2.1
	0 - 24	52.1 ± 7.2	3.9 ± 1.5	92.8 ± 3.2

In urinary excretion, both females and pregnant females show a higher excretion of unchanged levocetirizine than males.

Metabolites of [14C] levocetirizine following a single oral dose in rats, No. RRLE00C1503

Groups of 2/sex rats received orally 2 or 25 mg/kg of [14C] levocetirizine administered in an isotonic aqueous solution (2 ml/kg). Urine was collected at 8, 24 and 48 hr and feces were collected at 24 and 48 hr post dosing. The animals were sacrificed at 48 hrs. Metabolites were profiled using HPLC with radiometric detection. The 48 hr excretory pattern for the two doses in males and females is shown in the following table excerpted from the submission. The major excretory route in both sexes (M1, M2; F11, F12) was fecal. However, urinary excretion in females was greater than males.

Balance of excretion (0-48h) of radioactivity following oral administration of [^{14}C]-ucb 28556 at target doses of 2 and 25 mg/kg (results expressed as % dose)

2mg/kg	M1	M2	Mean	F11	F12	Mean
Urine	9.1	7.2	8.2	14.2	13.2	13.7
Faeces	98.6	109.2	103.9	72.7	93.5	83.1
Cage wash	0.23	0.57	0.4	1.32	0.23	0.8
Debris	NS	NS		NS	1.32	
Total	107.9	117.0	112.5	88.3	108.2	98.3

25 mg/kg	M21	M22	Mean	F31	F32	Mean
Urine	7.69	15.92	11.8	36.2	38.56	37.4
Faeces	88.3	73.2	80.7	76.4	39.62	58.0
Cage wash	0.22	0.55	0.4	0.70	3.49	2.1
Debris	NS	NS		NS	NS	
Total	96.2	89.6	92.9	113.3	81.7	97.5

NS = no sample

Retention and balance of excretion of [14C] levocetirizine in rats following a single oral dose, No. RRLE97C0601

Groups of 5 male, 5 female and 5 pregnant rats received by gavage, a single dose of 2 and 25 mg/kg of radioactive levocetirizine. Pregnant rats received levocetirizine on day 14 of gestation. Radioactivity was measured in urine and feces collected up to 168 hr in males and non-pregnant females and up to 96 hr in the pregnant animals. At necropsy, radioactivity was measured in blood, gastrointestinal tract (GIT), liver and carcass. The results showing the percent of the dose excreted in the urine are shown in the following table excerpted from the submission. At necropsy both non-pregnant females and pregnant rats show the excretory routes to be urinary and fecal as compared to mainly fecal for the males.

The amounts of radioactivity (% of the dose) excreted or measured at the time of sacrifice, are summarized in the following table :

Parameter	Males n=5	Females n=5	Pregnant females n=5
2 mg/kg			
Urine	12.5 ± 3.3	33.0 ± 9.9	36.4 ± 8.0
Cage wash	0.28 ± 0.13	0.96 ± 0.68	1.15 ± 1.45
Faeces	82.8 ± 12.5	64.2 ± 10.3	61.0 ± 14.0
Debris	21.0 ± 28.9	1.85 ± 3.57	11.15 (n = 2)
Balance	112.4 ± 14.8	99.7 ± 4.3	103.1 ± 8.1
Whole blood	0.09 ± 0.06	0.13 ± 0.04	0.14 ± 0.02
GIT	0.03 ± 0.04	0.02 ± 0.03	0.05 ± 0.01
Liver	0.08 ± 0.05	0.02 ± 0.01	0.06 ± 0.01
Carcass	0.18 ± 0.40	0.46 ± 0.27	0.38 ± 0.35
Retention	0.38 ± 0.37	0.53 ± 0.33	0.62 ± 0.35
Total	**113 ± 5**	**100 ± 4**	**104 ± 8**
25 mg/kg			
Urine	17.3 ± 5.0	64.0 ± 3.0	59.2 ± 6.1
Cage wash	0.33 ± 0.04	1.12 ± 1.03	1.45 ± 1.22
Faeces	96.8 ± 15.1	39.9 ± 4.1	38.8 ± 4.4
Debris	0.83 (n = 2)	0.35 ± 0.32	0.08 ± 0.08
Balance	114.7 ± 10.6	105.2 ± 2.1	99.5 ± 3.3
Whole blood	0.08 ± 0.05	0.04 ± 0.04	0.05 ± 0.03
GIT	0.07 ± 0.05	0.03 ± 0.02	0.07 ± 0.02
Liver	0.10 ± 0.06	0.03 ± 0.00	0.04 ± 0.02
Carcass	< BG	0.17 ± 0.38	0.18 ± 0.39
Retention	0.26 ± 0.07	0.26 ± 0.39	0.34 ± 0.40
Total	**115 ± 11**	**106 ± 2**	**100 ± 3**

Absorption distribution, metabolism and elimination of [14C] levocetirizine after oral administration to Beagle dogs, No. RRLE99L1301

The study was conducted in Beagle dogs; two males and 2 females received single or 8 daily oral radioactive doses of 1 mg/kg. Radioactivity was determined in urine and feces up to 48 hr following the administration of the single and 8th dose. The urinary and fecal excretion is shown in the following table excerpted from the submission. Excretion was fecal followed by urinary.

The amounts of radioactivity (% of the dose) excreted in urine and faeces or measured at the time of sacrifice, are summarized in the following table :

Parameter	Time of sacrifice							
	Single administration				Repeated administration			
	2h	6h	24h	48h	2h	6h	24h	48h
Urine	3.0	5.8	23.0	17.1	22.5	21.3	24.9	35.1
Cage wash	NS	NS	0.8	2.6	0.7	0.6	4.3	5.3
Faeces	NS	NS	14.1	57.0	48.8	62.6	56.4	63.2
Debris	NS	NS	1.7	3.0	2.4	2.0	2.2	2.6
Excretion	3.0	5.8	39.7	79.7	74.4	86.5	88.0	106.2
GIT*	15.8	12.1	38.8	5.6	4.5	3.4	4.2	1.5
Tissues**	89.0	78.7	20.5	3.6	14.3	10.7	2.3	1.4
Retention	104.8	90.8	59.3	9.2	18.8	14.1	6.5	2.9
Balance	**108**	**97**	**99**	**89**	**93**	**101**	**94**	**109**

* : including contents
** : including whole-blood
NS : no sample

GIT: gastrointestinal tract.

In the dog, levocetirizine administered as single or multiple doses is excreted mainly in the feces and urine.

2.6.4.7 Pharmacokinetic drug interactions: NA

2.6.4.10 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

In dogs, the pharmacokinetics were similar following single or multidose administration. Its absorption is by diffusion in the cell. In pregnant rats, plasma radioactivity levels depending the dose; at a low dose, plasma levels in pregnant animals are comparable to the levels in non-pregnant animals and higher than in males. At a high dose, the plasma levels in pregnant rats are higher than the non-pregnant and male rats.
Distribution studies in rats and dogs show significant levels in the liver and kidneys and very low levels in the brain below the background (rats) and in dogs high based on the ratio of the brain tissue radioactivity to the plasma unbound levocetirizine levels.
Levocetirizine is extensively metabolized in both rats and dogs. P450 enzymes are involved in the metabolism. In rats, the main metabolites are M1, M2, F11 and F12, and in dogs, the major metabolites were M7 +M8 and M10. Excretion in rats is mainly fecal in male, and fecal and urinary in females, while in dogs, excretion is fecal and urinary.

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Acute toxicities were conducted in mice rats and dogs. In mice and rats, the toxicity was determined by the oral and intravenous routes. By the oral route, the doses in mice were 240, 560, 1300 and 3200 mg/kg. All doses showed toxic signs beginning with quiet behavior, jerky breathing, ptosis, arched back and piloerection at 240 mg/kg. As the doses increased the toxicity increased leading to death at 560 (3/10) mg/kg and at 1300 (8/10). At 3200 mg/kg, the animals manifested cyanosis prior to death. By the intravenous route, the doses were 130, 190, 270 and 390 mg/kg. At all doses there was tail necrosis at the site of injection except at 390 mg/kg in which death was fairly quickly. At 190 mg/kg, there were signs of toxicity manifested by quiet behavior, jerks, tachynpea breathing, ventral lying position and unsteady gait, but no mortality. At 270 mg/kg, 8/10 and at 390 mg/kg all mice (10/10) died within 1-2 minutes. In another study, the acute intravenous toxicity of levocetirizine, S-cetirizine and cetirizine were compared. The toxicity profile of the three compounds was similar. However, the incidence of mortality was similar to levocetirizine and cetirizine and both of their incidences at lower doses were lower than S-cetirizine.
In rats, the oral doses were 100, 240 560 and 1300 mg/kg. Signs of toxicity were seen at 240 mg/kg as manifested by bradynpea, jerky breathing, ptosis, piloerection, ventral lying position, muscle weakness, dyspnea, muscle hypertonicity and soiled perineal region and no mortality. At 560 mg/kg, 7/10 rats died. They also showed extension of posterior paws, cyanosis, congested lungs, congested or hemorrhagic stomachs with necrotic glandular cell necrosis in the mucosa, thymus with red spots and intestines filled with bloody mucus. At 1300 mg/kg, 10/10 rats died. They also showed in addition to those seen at 570 mg/kg tremors and hypothermia. By the intravenous route, the doses were 32, 47, 68 and 100 mg/kg. At 32 mg/kg, the site of injection was discolored; there were no deaths. At 47 mg/kg, the tail injection site was necrotic. Other signs were ventral lying position, unsteady gait, pedaling movements with the hind limbs, spreading hind limbs, jumping, jerky breathing, tachynpea, dyspnea, muscle weakness and blood at the nose and in the urine; 3/30 rats died. Similar results were seen at 100 mg/kg whereby all animals died within 6 minutes. Tail necrosis was not observed due to the rapid onset of death.
In the dog, the oral doses were 32, 100 and 320 mg/kg in the acute toxicity study. No toxicity was seen at 32 mg/kg; At 100 and 320 mg/kg, emesis and diarrhea were observed. Due to the emesis, higher oral doses were not pursued.
Multidose oral toxicity studies of 4- and 13- weeks were conducted in rats and dogs.
In a 4-week oral toxicity study of levocetirizine and S-cetirizine in rats with a 4-week recovery period, the doses were 25, 75 and 225 mg/kg for both compounds. Decreased

body weight gained were seen with both HD compounds (levocetirizine, -31%; S-cetirizine, -27%). Hematological and clinical chemistry changes seen with both compounds were not treatment related, since they were not seen in the 13-week oral toxicity study. In males, both levocetirizine and S-cetirizine at the MD and HD induced enzyme induction as evidence by increased liver weight, hepatic centrilobular and midzonal enlargement and increased hepatic levels of microsomal protein, cytochrome P-450, ethylmorphine N-demethylase and p-nitroanisole O- demethylase and of 7-ethoxyresorufin O-deethylase; at the lowest dose, levocetirizine also increased levels of 7-ethoxyresorufin O-deethylase, and S-cetirizine also increased levels of cytochrome P-450. In males, both compounds produced hepatic centrilobular and midzonal fat and vacuolation. Levocetirizine also produced increased fat deposits in the renal cortical tubules which was not treatment related since this histopathology was not seen in the 13 week studies. All these changes were reversible. The liver was the target organ which showed enzyme induction, hepatic centrilobular and midzonal fat and vacuolation. Enzyme induction is not clinically relevant. These findings seen with levocetirizine and S-cetirizine were similar to those seen with cetirizine.

A 13-week oral toxicity study was conducted with levocetirizine in rats with a 4-week recovery period; the doses were 4, 8, 25 and 75 mg/kg. The only clinical sign was salivation. The increase in urinary protein (+31% in females and +48% in males) was not treatment related since it was not confirmed in a second 13-week oral toxicity study. Histologically, only males were affected as there was a reversible increase in the incidence of central lobular vacuolation and central lobular hypertrophy at the 25 and 75 mg/kg and an increased incidence of central fat deposition at 75 mg/kg. In males, there was an increase in enzyme induction of cytochrome P-450, aniline hydroxylase, β-Nitroanisole O- demethylase, ethylmorphine N-demethylase and 7-Ethoxyresorufin O-deethylase in males. The liver was the target organ which showed enzyme induction, hepatic centrilobular and midzonal fat and vacuolation. The changes were reversible. Enzyme induction is not toxicologically relevant. These findings seen with levocetirizine were similar to those seen with cetirizine indicating a similar toxicity profile for both compounds.

A 13-week oral toxicity study was conducted with levocetirizine and cetirizine in rats with a 4-week recovery period. The doses were 18.7, 37.5 and 75 mg/kg for levocetirizine and 37.5 and 75 mg/kg for cetirizine. Both compounds had no effect on the imunoglobulins, IgA, IgG and IgM, and lymphocyte subsets. Histologically, both compounds produced in males a reversible increase in the incidence of hepatic central lobular hypertrophy and central fat deposition. This confirms the hepatic fat deposition seen with cetirizine in the 2-year carcinogenicity study. The overall toxicity profile for both compounds was similar in rats.

In dogs, a 4-week oral toxicity was conducted with levocetirizine and S-cetirizine using doses of 15, 45 and 135 mg/kg. The 135 mg/kg dose of levocetirizine was toxic requiring 1 male and 2 females to be killed on days 1, 8 and 9 in a moribund condition. On day 9 the dose was lowered to 90 mg/kg. Among the toxic symptoms seen in these animals were tremors, fecal impaction, hypothermia, abnormal gait and elevated enzymes. Both compounds were emetogenic at the MD and HD. The HD-levocetirizine treated males showed a 50% increase in urine volume. This was not seen in another 4-week study at the same dose. Other than emesis in the lower dosed animals for both compounds, there was

no other toxicity. The target organ was the gastrointestinal tract. Levocetirizine was more toxic than S-cetirizine

In a second 4-week oral toxicity study with a 4-week recovery period, cetirizine was tested along with levocetirizine and S-cetirizine. The oral doses were 33.75, 67.5 and 135 mg/kg for levocetirizine and S-cetirizine and 135 mg/kg for cetirizine. Due to severe toxicity, two 135 mg/kg levocetirizine treated animals were killed in a moribund condition, one on day 9 and the other on day 17. One cetirizine treated dog was killed in a moribund condition on day 9. On days 11 day 18, the dose of levocetirizine and cetirizine was lowered 90 mg/kg. The toxicity for the HD levocetirizine and cetirizine were similar, i.e., emesis, tremors and fecal impaction. The HD for S-cetirizine produced a toxicity profile similar to levocetirizine although not severe enough to lower the dose. Emesis was seen in all doses of the levocetirizine, S-cetirizine and cetirizine treated animals. Levocetirizine at the HD in males produced an increase in the Qtc by 15%. This was not confirmed in the first oral 4-week study at the same dose. In two 13-week studies discussed below, where the HD was lower (75 mg/kg vs. 135/90 mg/kg), there was no increase in the Qtc in the first study and in the second study there was at 13-weeks a 7% increase in the Qtc in females of both levocetirizine and cetirizine treated dogs. This slight increase is not considered toxicologically significant. The HD female with levocetirizine showed a 93% increase in eosinophils. This was not confirmed at the same dose in another 4- week toxicity study. Fecal impaction was seen 2/6 in the 37.5 mg/kg and 135/90 mg/kg levocetirizine treated animals and in 2/5 animals in the 135/90 mg/kg cetirizine group. Histology showed mucosal atrophy of the trachea in 2/3 male dogs in the 135/90 mg/kg levocetirizine treated animals. This was not confirmed in another 4-week oral study.

A 13-week oral toxicity in dogs was conducted with levocetirizine; the doses were 8, 25 and 75 mg/kg. Emesis occurred in all doses in females and at the HD in males. EKG, hematological, urinary and clinical chemistry changes were not seen in another 13-week oral study. Absolute spleen weight was increased at MD and HD mg/kg which was not supported by histopathology or confirmed in another 13-week study. There were no histopathological findings.

A second 13-week oral toxicity study was conducted with levocetirizine and cetirizine with a 4-week recovery period. The oral doses were 37.5 and 75 mg/kg for levocetirizine and 75 mg/kg for cetirizine. Emesis was seen with cetirizine and both doses of levocetirizine. Changes in the hematology and clinical chemistry and increased salivary weight were not confirmed in another 13-week study. Histologically, cetirizine at 75 mg/kg reduced spermatogenesis in males and produced inflammatory cells in the livers of females. Levocetirizine at 75 mg/kg produced increased small aggregates in Kupffler cells in the livers of HD females and at both doses in both sexes increased the incidence of inflammatory cells in the livers. These were not seen in another 13-week study. The toxicity profiles of cetirizine and levocetirizine are similar, and the target organ was the gastrointestinal tract.

Genetic toxicology:

Levocetirizine was not mutagenic in two Reverse Bacterial Mutation Assays and not genotoxic in two Mouse Lymphoma Assays and one Micronucleus Assay. Six Human

Lymphocyte Aberration assays were conducted. The first assay involved 2 tests in the absence and presence of S9. In the absence of S9, three studies were conducted. In the first study (116, 179 and 275 ug/ml, exposure time, 20 hr; harvest time, 0 hr), the test was invalid since the Mitotic Index was increased at the highest concentration by 63%. In the second study (168, 240 and 343 ug/ml, exposure time, 20 hr; harvest time, 0 hr), levocetirizine was positive, and the Mitotic Index was increased at the highest concentration by 37%.(The positive finding was not confirmed in the third assay, test No. 3, 300, 550, 600 and 650 ug/ml). A third test (240 ug/ml, exposure time, 3 hr; harvest time, 41 hr) was invalid since a positive control was not tested. In the first study involving the presence of S9, (275, 423 and 650 ug/ml, exposure time, 3 hr; harvest time, 17 hr), levocetirizine was negative at all concentrations and the results acceptable since the Mitotic Index was inhibited by 58% at the highest concentration. In the second study (240, 343 and 490 ug/ml, exposure time, 3 hr; harvest time, 17 hr), levocetirizine was negative at all concentrations. The Mitotic Index at the highest concentration was decreased by 64%. A third study (490 ug/ml, exposure time, 3 hr; harvest time, 41 hr) was invalid since a positive control was not included in the assay.

The second assay involved 2 tests in the absence and presence of S9. In the absence of S9, three studies were conducted. In the first study (38, 150 and 350 ug/ml, exposure time, 24 hr; harvest time, 0 hr), levocetirizine was positive at the highest concentration. The Mitotic Index at the highest concentration was decreased by 47%. The positive results were confirmed following reexamination of the slides by an outside laboratory. In the second study (150, 350 and 500 ug/ml, exposure time, 24 hr; harvest time, 0 hr), levocetirizine was negative at all concentrations, thereby not confirming the positive results in the first study. The Mitotic Index at the highest concentration was decreased by 55%. In the third study (39, 156 and 313 ug/ml, exposure time, 48 hr; harvest time, 0 hr) was invalid since a positive control was not tested. In the presence of S9, two studies were conducted. Both studies involved exposure time, 3 hr; harvest time, 21 hr. The concentrations were 78, and 63 and 625 in the first study and 78, 400 and 800 ug/ml and their respective inhibition of Mitotic Index was -75% and 60%. Positive results were seen at 625 ug/ml in the first test and 800 ug/ml in the second test. At lower concentrations, levocetirizine was negative. The slides from the 800 ug/ml concentration when reexamined by an outside laboratory confirmed the positive activity. However, these positive results occurred at high cytotoxic concentrations. At the lower concentrations, these results were negative indicating that levocetirizine was negative.

The third assay involved 2 studies both in the absence and presence of S9. In the two studies in the absence of S9 and the two studies in the presence of S9 which were valid studies, levocetirizine was negative at all concentrations. In the two studies in the absence of S9, the parameters were first study: 600, 650, and 700 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, 44%; second study: 300, 550, 600 and 650 ug/ml, exposure time, 20 hr; harvest time, 0 hr and inhibition of the Mitotic Index at the highest concentration, 65%. In the two studies in the presence of S9, the parameters were: first study: 400, 550 and 650 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, 47%; second study: 600, 650 and 700 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, 57%.

The fourth assay involved one study in the absence and one study in the presence of S9. In the absence of S9 (78, 250 and 350 ug/ml, exposure time, 20 hr; harvest time, 0 hr and increased Mitotic Index at the highest concentration, 139%), results were invalid since at the highest concentration, the Mitotic Index was enhanced and not inhibited. In the presence of S9 (60, 78, 313 and 625 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, -73), levocetirizine was negative at all concentrations.
The fifth assay involved 3 studies in the absence and 3 studies in the presence of S9. In the first study in the absence of S9, (116, 179 and 275 ug/ml, exposure time, 20 hr; harvest time, 0 hr), the test was invalid since the Mitotic Index was not cytotoxic at all. In the second study (117, 168 and 240 ug/ml, exposure time, 20 hr; harvest time, 0 hr), the Mitotic Index at the highest concentration was increased (94%) rather than inhibited; the test was invalid since the Mitotic Index was not cytotoxic. In the third study (240 ug/ml, exposure time, 44 hr; harvest time, 0 hr and the Mitotic Index at the highest concentration was inhibited (65%), the test was invalid since no positive control was included in the assay. In the presence of S9, the first study (275, 423 and 650 ug/ml, exposure time, 3 hr; harvest time, 17 hr), was not valid since the Mitotic Index at the highest concentration was not cytotoxic. The second study (343, 490 and 700 ug/ml, exposure time, 3 hr; harvest time, 17 hr) was negative. The third study (240 ug/ml, exposure time, 44 hr; harvest time, 0 hr), was not valid since no positive control was used in the test.
The sixth assay involved evaluation of Batches D005, D006 and D008 to determine whether there was a difference in the activity in this assay. The assay was not valid since positive controls were not included in the assay.
From the results of the six assays, levocetirizine was concluded as negative in the Chromosomal aberration assay since a positive response was not confirmed in several other Chromosomal aberration assays or a positive response occurred only at a high cytotoxic concentration, and the lower concentration was negative.

Reproductive toxicology:

In fertility and early developmental studies in rats, cetirizine was tested at oral doses up to 200 mg/kg in both sexes. Males were administered daily for 63 days before mating and through the mating period until the day before necropsy, and females were administered daily for 14 days before mating and through the mating period until 7 days of gestation. Semen was collected after copulation from the tail of the epididymis. Cetirizine did not affect sperm dynamics, male and female fertility and early fetal developmental.
Embryofetal developmental studies were conducted with levocetirizine and cetirizine in rats and rabbits. In pregnant rats, oral doses of 50, 100 and 200 mg/kg of levocetirizine and 200 mg/kg of cetirizine were administered from day 6 to day 15 of gestation and sacrificed on day 20. Two rats receiving cetirizine died or were killed for humane reasons that were treatment related. Levocetirizine and cetirizine at 200 mg/kg produced an 18% and 15%, respectively, decrease in body weight gained. Levocetirizine did not produce skeletal and visceral malformations, anomalies or skeletal variants. Cetirizine did not produce skeletal and visceral malformations or anomalies.

In pregnant rabbits, oral doses of 30, 60 and 120 mg/kg of levocetirizine and 120 mg/kg of cetirizine were administered from day 6 to day 18 of gestation and sacrificed on day 29. Three HD-levocetirizine treated animals died that were treatment related. Levocetirizine and cetirizine did not produce skeletal and visceral malformations. However, cetirizine produced a slight increase the incidence of skeletal variants.

Special toxicology:

A study was conducted to determine whether cetirizine, levocetirizine and S-cetirizine were cytotoxic to rat hepatocytes following 3 and 24 hr incubation. At 3 hr, all three compounds were equally cytotoxic with respective IC50s of 0.74, 0.63 and 0.67 mmol/L. In the 24 incubation only levocetirizine and S-cetirizine were tested. Both were equally cytotoxic with respective IC50s of 0.59 and 0.50 mmol/L.

2.6.6.2 Single-dose toxicity

Acute oral toxicity of levocetirizine (UCB28556) in the mouse (LD50), No. RRLE92C1003
Acute intravenous toxicity of levocetirizine (UCB28556) in the mouse (LD50), No. RRLE92E1301
Acute intravenous toxicity of levocetirizine (UCB28556), S-cetirizine (UCB28557) and cetirizine (ucb P071) in the mouse, No. RRLE87E131
Acute oral toxicity of levocetirizine (UCB28556) in the rat (LD50), No. RRLE92D2104
Acute intravenous toxicity of levocetirizine (UCB28556) in the rat (LD50), No. RRLE92F0303
Acute oral toxicity of levocetirizine (UCB28556) in the dog, No. RRLE92C1202

The results with levocetirizine are summarized in the following tables.

Species/Route Duration of Observation	Observations Dose, mg/kg
Mouse Oral 5/sex/group 14 Days	240, quiet behavior, jerky breathing, ptosis, arched back and piloerection, no gross pathology. Mortality: 0/10 560, quiet behavior, jerky breathing, ptosis, arched back and piloerection toe walking, muscle weakness, dyspnea, muscle hypertonicity and no gross pathology. Mortality: 3/10 1300, same as 560 plus tremors, ventral lying position, blood on nose, transient apnea, soiled perineal region, hypothermia, pale, marbled and congested livers and congested intestines and stomachs. Mortality, 8/10, 3200, same as 1300 plus cyanosis.
Intravenous 5/sex/group 14 Days	130, tail necrosis. Mortality: 0/10 190, quiet behavior, jerks, tachynpea breathing, ventral lying position unsteady gait, tail necrosis and no gross pathology. Mortality: 0/10 270, tail necrosis, exophthalmia, ventral lying position, spread hindlimbs, dyspnea, agitation, tachynpea breathing, hemorrhagic lungs. Mortality: 8/10. 390, exophthalmia, ventral lying position, spread hindlimbs. Mortality: 10/10; death occurred in 1-2 min.
Rat Oral 5/sex/group 14 Days	100, no effects. Mortality: 0/10 240, bradynpea, jerky breathing, ptosis, piloerection, ventral lying position, muscle weakness, dyspnea, muscle hypertonicity, soiled perineal region and no gross pathology. Mortality: 0/10 560, bradynpea, jerky breathing, ptosis, ventral lying position, muscle weakness, dyspnea, muscle hypertonicity soiled perineal region, extension of posterior paws, cyanosis, congested lungs, congested or hemorrhagic stomachs with necrotic glandular cell necrosis in the mucosa, thymus with red spots and intestines filled with bloody mucus. Mortality: 7/10 1300, same as 560 plus tremors, pedaling of posterior paws, piloerection, body contractions and hypothermia. Mortality: 10/10

Species/Route Duration of Observation	Observations Dose, mg/kg
Rat Intravenous 5/sex/group 14 Days	32, injection site became mauve which was reversible. Mortality, 0/10 47, ventral lying position, unsteady gait, pedaling movements with the hind limbs, spreading hind limbs, jumping, jerky breathing, tachynpea, dynpnea, muscle weakness, blood at the nose and in the urine, necrosis at injection site and no gross pathology. Mortality: 3/10. 68, same as 47 mg/kg plus agitation 100, same as 47 except no necrosis at the injection site. Mortality, 10/10 within 6 min.
Dog Oral 1/sex/group 14 Days	32, no effect. 100 and 320, emesis, diarrhea. Because of the emesis, higher doses were not tested.

Acute intravenous toxicity of levocetirizine, S-cetirizine and cetirizine in the mouse, No. RRLE87E131

A comparison of the acute toxicity of levocetirizine, S-cetirizine and cetirizine was determined in mice, Groups of 5 mice/sex (males, 17-20 g; females, 17-20 g) were used. They were observed daily for 14 days. All three compounds in both sexes the following similar clinical signs: unsteady gait, dyspnea, decreased motor activity, jerks, side lying paddling movements, tremors and death. At the high doses, most deaths occurred within 10 minutes. At the lower doses, death occurred less than 6 days.

Dose, mg/kg Intravenous	Incidence of Mortality					
	Levocetirizine		S-cetirizine		Cetirizine	
	Males	Females	Males	Females	Males	Females
180	-	-	0/5	1/5	-	-
240	0/5	0/5	2/5	1/5	0/5	0/5
320	0/5	1/5	5/5	5/5	2/5	1/5
420	5/5	5/5	5/5	5/5	5/5	5/5
560	5/5	5/5				

The incidence of mortality is comparable with levocetirizine and cetirizine and higher than S-cetirizine. There was no difference to the incidence of mortality between levocetirizine and cetirizine. The gross findings were negative.

2.6.6.3 Repeat-dose toxicity

Study titles: **Four week oral toxicity of levocetirizine and S-cetirizine in rats with a 4-week recovery period.**

Key study findings:

- For levocetirizine and S-cetirizine, males show reversible increased hepatic hypertrophy at the MD and HD associated with enzyme induction as evidenced by increased levels of microsomal protein, cytochrome P-450, ethylmorphine N-demethylase and p-Nitroanisole O-demethylase. At LD, levocetirizine produced increased levels of 7-ethoxyresorufin O-deethylase, and S-cetirizine increased levels of cytochrome P-450.
- In the MD and HD males, levocetirizine and cetirizine produced centrilobular hepatic enlargement and midzonal vacuolation and fat deposits.
- In the LD, MD and HD males, levocetirizine and S-cetirizine produced enzyme induction which is species specific and not clinically relevant.
- The liver was the targeted organ for levocetirizine and S-cetirizine.
- These findings are similar to those of cetirizine in rats.

Study no.: No. RRLE95C1401 (TX001).
Conducting laboratories and locations: Toxicological Laboratories UCB S.A. Pharma Sector, Belgium

Date of study initiation: 3/9/91.
GLP compliance: Yes.
QA report: yes (X) no ( )
Drugs, Batch #, and % purity: Levocetirizine D005,

Methods

Doses: 0 (Purified water, 10 ml/kg) Levocetirizine, 25, 75 and 225 mg/kg, orally
S-cetirizine, 25, 75 and 225 mg/kg, orally
Species/strain: SPF Sprague Dawley OFA rats/
Number/sex/group or time point (main study): 12.

Satellite groups used for toxicokinetics: recovery group C and HD, 6/sex/group.
Age: 4-5 weeks.
Mean weight range/group: Males 320-325 g; females, 236-244 g.
Sampling times: 0, 1.5, 3, 6, 9, and 12 hr post dose on day 23.
Unique study design or methodology (if any): None.

Observations:
Mortality: Daily.
Clinical signs: Daily.
Body weights: Weekly.
Food consumption: Twice a week.
Ophthalmoscopy: Pre-test and Week 4, C and HD.
Hematology: Week 5 and week 9 in the recovery group.
Clinical chemistry: Week 5 and week 9 in the recovery group...
Urinalysis: Days 1 and 17.
Gross pathology: Week 5 and week 9 in the recovery group.
Organ weights: See histopath table.
Toxicokinetics: Blood was removed at 1.5, 3, 6 and 9 hr post dose on day23.
Histopathology: Gross abnormal tissue and tissues listed in the histopath table from C and HD.
Livers: Samples of liver tissues was assayed for microsomal protein, and various enzymes, cytochrome P-450, p-Nitroanisole O- demethylase, ethylmorphine N-demethylase and 7-Ethoxyresorufin O-deethylase.

Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

Results

Mortality:
Levocetirizine:
Males: HD, 3/12; females, MD, 2/12: HD mg/kg, 5/12. Recovery group: Male: HD, 2/6; Female, C, 1/6; 3/6. Animals died a short time following oral administration due to technical dosing error or technical error following blood sampling since in the 13-wk oral

study, animals receiving the same MD did not produce mortality or the toxic signs (labored breathing, congested lungs and blood-like nasal discharge) seen in this study.
S-cetirizine
Males: MD, 1/12; Females, 3/12; Males, HD, 1/12; females HD, 4/12. These deaths were also due to a technical error and are not considered treatment related.

Clinical signs: Intermittent salivation in both sexes at all doses.

Body weight gained: Levocetirizine: HD, males, -31%; females, no change. Full recovery.

S-Cetirizine: HD, males, -27%; females, no change. Full recovery.

Food consumption: No change.

Hematology and Clinical Chemistry

The results are summarized in the following table. These changes were not seen in the two 13-week toxicity studies in rats and are not considered levocetirizine related.

Parameter	**% Change at HD**			
	Levocetirizine		**S-cetirizine**	
	Males	**Females**	**Males**	**Females**
Urea	+20	0	0	0
Cholesterol	+21	0	0	0
Triglycerides	-40	0	-62	30
Phospholipids	+18	0	-22	0
A2 Globulin	+18	+18	+28	0
Platelets	+20	+27	-22	0

Recovery Period, Week 9: S-cetirizine, platelets, 29%. There was recovery from the other changes.

Urinalysis: No change.

Toxicokinetics and urinary excretion (Ae) of levocetirizine and S-cetirizine expressed as percent of the dose on day 17 are presented in the following table is excerpted from the submission.

	Levocetirizine			S-cetirizine		
	ucb 28556			ucb 28557		
Dose : mg/kg/day	25	75	225	25	75	225
Cmax (µg/ml, Day 23)						
M	17.3	80.8	80.7	2.8	16.0	51.5
F	12.4	44.8	127.8	5.3	16.3	29.1
$AUC_{0-24\,h}$ (µg.h/ml, Day 23)						
M	88.8	386.8	1004.6	5.0	90.6	347.5
F	40.7	198.9	1010.0	8.9	65.9	204.7
Ae (% dose, Day 17)						
M	11.7	27.4	42.7	1.5	20.9	20.9
F	38.1	57.7	58.9	32.6	53.5	50.9

Levocetirizine at comparable doses show higher Cmaxs and AUCs than S-cetirizine. Both levocetirizine and S-cetirizine are similar in being excreted in the urine. However, The urinary excretion of levocetirizine and S-cetirizine was higher in females than in males.

Gross Pathology: None.

Organ weight:
Liver: Levocetirizine: Males, Absolute wt., HD, +23%
Relative wt. MD, +11%; HD, +42%
End of recovery period: Complete recovery.
Females: Absolute wt., HD, no change.
Relative wt. HD, +16%
End of recovery period: Complete recovery.
S-cetirizine: Males, Absolute wt. MD, +22%; HD, +38%
Relative wt. MD, +16%; HD, +56%
End of recovery period: Complete recovery.
Females: Absolute wt. HD, +24%
Relative wt. HD, +30%
End of recovery period: Complete recovery.

Liver enzymes (based on per g of liver or mg of microsomal protein): For females:
S-cetirizine: p-Nitroanisole O-emethylase, MD, +59%; HD, +169%.
For males, the results indicate that males are more responsive to induction as shown in the following table.

Dose, mg/kg, Orally	% (P<0.05) Increase from Controls (males)				
	Microsomal Protein	**Cytochrome P-450**	**Ethylmorphine N-demethylase**	**p-Nitroanisole O-demethylase**	**7-Ethoxyresorufin O-deethylase**
Levocetirizine					
LD	0	0	0	0	33
MD	39	170	72	67	224
HD	140	493	78	142	296
S-cetirizine					
LD	0	62	0	0	0
MD	76	125	81	81	162
HD	176	605	200	375	375

There was full recovery.

Histopathology

The histopathological changes observed with levocetirizine are presented in the following table. The data for the LD in males are not presented as there was no histopathology. The kidney changes are not treatment related since they were not seen in the 13-week toxicity study. The liver is the targeted organ of toxicity showing the same profile as cetirizine.

Organ/ Observation	Incidence, N=12/13						
	Males			Females			
	C	**MD**	**HD**	**C**	**LD**	**MD**	**HD**
Liver							
Centrilobular enlargement	0	3	5	0	0	0	1
Centrilobular vacuolation	0	0	4	0	0	0	0
Centrilobular fat	0	2	3	0	0	0	0
Centrilobular and midzonal enlargement	0	1	8	0	0	0	0
Midzonal vacuolation	0	0	5	0	0	0	0
Midzonal fat deposits	0	1	10	0	0	0	0
Kidneys							
Fat deposits in cortical tubules	0	3	4	3	7	2	7

The histopathological changes observed with S-cetirizine are presented in the following table. The data for the LD were not presented as there were no incidences. The liver is the target organ of toxicity.

Organ/ Observation	Incidence, N=12/13					
	Males			Females		
	C	MD	HD	C	MD	HD
Liver						
Centrilobular and midzonal enlargement	0	1	12	0	0	0
Midzonal vacuolation	0	1	3	0	0	0
Midzonal fat deposits	0	1	8	0	0	0

End of recovery period: Reduced incidence or complete recovery.

Study titles: **13-Week oral toxicity in rats of levocetirizine with a 4-week, recovery period**

Key study findings:

- In males, reversible increased incidence of hepatic central lobular vacuolation and lobular hypertrophy at the HD and VHD and fat deposition at the VHD.
- Reversible increase in males in enzyme induction of cytochrome P-450 (VHD), β-Nitroanisole O- demethylase, ethylmorphine N-demethylase and 7-Ethoxyresorufin O-deethylase (HD and VHD)and aniline hydroxylase (all doses). Enzyme induction is species specific and is not clinically relevant.
- Liver was the target organ of toxicity and the changes were reversible.
- There was no evidence of the inversion of levocetirizine to S-levocetirizine.
- The toxicity profile of levocetirizine was similar to cetirizine.

Study no.: **No. RRLE98H2402 (UCB412) and RRLE98H2403.**

Conducting laboratories and locations: (b) (4) and and UCB S.A. Pharma Sector, Laboratory of Drug Metabolism and Pharmacokinetics Research and Development, Belgium (plasma and urine analyses) and Chrysalis, France (lymphocyte)
Date of study initiation: 12/30/91
GLP compliance: Yes.
QA report: yes (X) no ( )
Drugs, Batch #, and % purity: D006, 100.3%

Methods

Doses: 0 (Distilled water, 5 ml/kg) Levocetirizine, 4 (LD), 8 (MD), 25 (HD) and 75 (VHD) mg/kg.
Species/strain: Crl: CD (SD) BR VAF/Plus rats.
Satellite groups used for toxicokinetics: 5/sex/group; recovery group C and HD, 5/sex/group.
Age: 28 days old.
Mean weight range/group: Males 163-169 g; females, 95-96 g.
Sampling times: 0, 1.5, 3, 6, 9, and 12 hr post dose.

Unique study design or methodology (if any): None.

Observations:

Mortality: Daily.
Clinical signs: Daily.
Body weights: Day 0 and weekly.
Food consumption: Weekly.
Water consumption: Daily.
Ophthalmoscopy: Weeks 13 and 17.
Hematology: Weeks 13 and 17. Week 13: Lymphocytes, CD5+, B, lymphocytes, CD+4 CD+8, CD+4, CD4+ CD8, CD+25 and Natural killer cells were counted.
Clinical chemistry: Weeks 13 and 17.
Urinalysis: Weeks, 1, 6 and 13.
Gross pathology: Weeks 13 and 17.
Organ weights (see histopath table):
Histopathology: Gross abnormal tissue and tissues listed in the histopath table from C and HD.
Livers: Tissues of all groups were stained for fat with Oil Red O at weeks 13 and 17. Another sample of liver tissues was assayed for microsomal protein, cytochrome P-450, aniline hydroxylase, β-Nitroanisole O- demethylase, ethylmorphine N-demethylase and 7-Ethoxyresorufin O-deethylase.

Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

Results

Mortality: None.

Clinical signs: Salivation: Incidence of post dosing (percent/week), C, 0%; VHD, Males, 11%; Females 5%.

Body weight gained: No effect.

Food consumption: No effect.

Water consumption: No effect.

Ophthalmoscopy: No effect.

Hematology: No effect; lymphocyte subsets: No effect.

Clinical chemistry: No effect.

Urinalysis: Protein, VHD, Males, +31%; Females, +48%. Recovery group: Reversible. This was not treatment related since it was not confirmed in a second 13-week oral toxicity study.

Toxicokinetics: Levels were detectable at 0.1 mcg/ml.

	4 mg/kg		8 mg/kg		25 mg/kg		75 mg/kg	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Cmax (ug/ml)	1.71	1.23	5.48	3.55	21.2	16.6	72.5	89.0
Tmax, (hrs)	1.5	1.5	3.0	1.5	1.5	1.5	1.5	1.5
$AUC_{0\text{-}24\ hr}$ (ug.hr/ml	3.08	1.98	32.5	10.6	107	46.8	441	386

Urinary Excretion
Urinary excretion in females play a major role in the excretion of levocetirizine as seen in the following table. There was no evidence of inversion of levocetirizine to the S-levocetirizine.

Week	**% of Oral Dose Administered**							
	4 mg/kg		**8 mg/kg**		**25 mg/kg**		**75 mg/kg**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
1	0.04	3.1	0.31	22.6	6.9	29.0	22.3	31.1
6	0.49	1.5	0.81	26.1	15.4	28.4	26.4	36.5
13	0.24	5.3	1.7	28.9	23.7	23.7	23.9	36.7

Gross pathology: None.

Organ weights: No effect.

Histopathology:

Organ Pathology	Incidence									
	Control		4 mg/kg		8 mg/kg		25 mg/kg		75 mg/kg	
	M	F	M	F	M	F	M	F	Male	F
Liver										
Central Lobular Vacuolation	2/10	0/10	1/10	1/10	1/10	0/10	5/10	0/10	8/10	0/10
Central Lobular Hypertrophy	0/10	0/10	0/10	0/10	0/10	0/10	4/10	0/10	7/10	0/10
Central Fat Deposition[a]	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	6/10	0/10

[a] Determined with Oil red stain

These liver findings confirmed those seen in the 4-week oral toxicity study in rats. The liver changes were reversible.

Liver, enzyme analysis: There was no change in microsomal protein. The following table shows that there was an increase in cytochrome P450, aniline 4-hydroxylase, p-nitroanisole O-demethylase, ethylmorphine N-demethylase (CYP3AT) and 7-ethoxyresorufin O-deethylase. These effects were reversible.

Parameter	Relative to the Mean Control Group (nmoles/g of liver) Taken as(1)									
	4 mg/kg		8 mg/kg		25mg/kg		75 mg/kg		75 mg/kg	
	M	Female	M	F	M	F	Male	F	M	F
									Recovery	
Cytochrome P4540	NC	0.7	NC	0.8	NC	0.7	2.6	0.9	NC	NC
Aniline hydroxylase	NC	NC	NC	NC	1.5	NC	1.6	NC	NC	NC
p-Nitroanisole O-demethylase	1.1	NC	1.2	NC	2.2	NC	3.5	NC	NC	NC
Ethylmorphine N-demethylase	NC	NC	NC	NC	1.6	NC	1.5	NC	NC	NC
7-Ethoxyresorufin O-deethylase	NC	NC	NC	NC	3.7	NC	5.0	NC	NC	1.3

NC, No change from control

Study title: **13-Week oral toxicity in rats of levocetirizine compared with cetirizine with a 4-week, recovery period**

Key study findings:

- Levocetirizine induced two or more enzymes at 18.5, 37.5 and 75 mg/kg, orally and cetirizine induced one or more enzymes at 37.5 and 75 mg/kg, orally. Enzyme induction is rodent species and not clinically relevant.
- Levocetirizine and cetirizine produced in males hepatic central lobular hypertrophy at 75 mg/kg.
- Levocetirizine produced hepatic central fat deposition at18.5, 37.5 and 75 mg/kg while cetirizine increased hepatic central fat deposition at 37.5 and 75 mg/kg.
- Liver was the targeted organ.
- Levocetirizine and cetirizine possess a similar toxicity profile in this 13-week toxicity study in rats.

Study no.: No. RRLE98H2402 (TA0283).
Conducting laboratory and location: (b) (4)
Date of study initiation: 7/4/96
GLP compliance: Yes.
QA report: yes (X) no ( )
Drugs, Batch #, and % purity: Levocetirizine, # 100, 99.3%, 99.97%; cetirizine, # C95365-2233, 99.65%

Methods

Doses: 0 (distilled water, 5 ml/kg) Levocetirizine, 18.7, 37.5 and 75 mg/kg; cetirizine, 37.5 and 75 mg/kg.
Species/strain: Crl: CD (SD) BR rats.
Number/sex/group or time point (main study): C and HD, 15; LD and MD 10.
Route, formulation, volume: Oral, distilled water, 5 ml/kg.
Satellite groups used for toxicokinetics or recovery: toxicokinetics, 5/sex/group; recovery, C and HD, 5/sex/group.
Age: 42 days.
Weight: Males, 186-229 g; females, 139-181 g.
Sampling times: 0, 1.5, 3, 6, 9, and 12 hr post dose.
Unique study design or methodology (if any): None.

Observations and times:
Mortality: Daily.
Clinical signs: Daily.
Body weights: Day 0 and weekly.
Food consumption: Weekly.
Water consumption: Daily during week 12/13.
Ophthalmoscopy: Prior to initiating dosing and during week 13.
Rectal temperature: Weeks, -1, 4, 8 and 13 prior to and 3 hr post dose.
Hematology: Weeks 13 and 17.
Immunoglobulins (IgA, IgG and IgM): Week 13.

Lymphocytes subsets (T (CD5) cells, B cells, helper T (CD4) cells, suppressor/cytotoxic T (CD8) cells, activated T (CD25) cells, immature T cells and natural killer cells: Week 13.
Clinical chemistry: Weeks 13 and 17.
Urinalysis: Weeks 13 and 17.
Gross pathology: Weeks 13 and 17.
Organ weights (specify organs weighed if not in histopath table):
Histopathology: Gross abnormal tissue and tissues listed in the histopath table from C and HD, levocetirizine, and cetirizine groups.
Livers: Tissues were stained for fat with Oil Red O.
Sperm analysis at all stages of the sperm cycle: Methodology was not described.

Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )

Results

Mortality: Females, C, 1; Levocetirizine, MD (recovery group), 1; cetirizine, HD, 1. Deaths were not treatment related due to technical error.

Clinical signs: Levocetirizine and cetirizine: None.

Body weight gained: Levocetirizine and cetirizine: No effect.

Food consumption: Levocetirizine and cetirizine: No effect.

Water consumption: Levocetirizine and cetirizine: No effect.

Rectal temperature: Levocetirizine and cetirizine: No effect.

Ophthalmoscopy: Levocetirizine and cetirizine: No effect.

Hematology: No effect.

Clinical chemistry: No effect.

Immunoglobulins (IgA, IgG and IgM): Levocetirizine and cetirizine: No effect

Lymphocyte Subsets: Levocetirizine and cetirizine: No effect.

Urinalysis: Levocetirizine and cetirizine: No effect

Gross pathology: Levocetirizine and cetirizine: None.

Organ weights: Levocetirizine and cetirizine: No effect.

Toxicokinetics: The report indicated that the data was suspicious probable due to mislabeling of samples, necessitating repeating a 13-week oral study in rats.

Hepatic enzyme analysis

The results are summarized in the following table.

Enzyme	Relative to the Mean Control Group (nmoles/g of liver) Taken as(1)									
	Cetirizine				Levocetirizine					
	37.5 mg/kg		75 mg/kg		18.5 mg/kg		37.5 mg/kg		75 mg/kg	
	M	F	M	Female	Male	F	M	F	M	F
Microsomal protein, mg/g of liver	NC	NC	1.2	NC	NC	NC	NC	NC	NC	NC
Cytochrome P450 nmoles/mg protein	NC	NC	1.3	NC	NC	NC	NC	NC	1.2	NC
CYP1A	2.7	NC	4.1	NC	NC	NC	NC	NC	3.6	NC
CYP2B	NC	NC	3.3	13.1	NC	NC	NC	NC	NC	NC
CYP2A	NC	NC	3.4	NC	NC	NC	NC	NC	NC	NC
CYP2B	NC	NC	1.7	NC	1.3	NC	1.4	NC	1.7	NC
CYP2C	NC	NC	1.5	NC	NC	NC	1.3	NC	1.6	NC
CYP3A	NC	NC	1.3	1.3	1.2	NC	1.2	NC	1.3	NC
CYP2E	NC	NC	1.3	NC	NC	NC	NC	NC	NC	NC
CYP4A	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
p-Nitro UDP glucuronyl-trasnsferase	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

NC, No change

The above findings were reversible.

Histopathology:

Cetirizine Levocetirizine

Organ Pathology	Incidence in Males					
	Control	37.5 mg/kg orally	75 mg/kg orally	18.5 mg/kg orally	37.5 mg/kg orally	75 mg/kg orally
Liver Central Lobular Hypertrophy	0/10	0/10	5/10	0/10	0/10	5/10
Central Fat Deposition[a]	1/10	2/10	9/10	3/10	3/10	5/10

[a] Determined with Oil red stain

The liver findings were reversible.

The hepatic hypertrophy seen with levocetirizine and cetirizine was a reflection of the enzyme induction confirmed by the presence of increased liver enzymes. The fat deposition is a cetirizine treatment related manifestation as it was also seen in the 2-year carcinogenicity study in rats.

Study title: 4-Week oral toxicity of levocetirizine and S-cetirizine in dogs.

Key study findings:

- The HD (135 mg/kg) for levocetirizine was lethal, requiring the oral dose to be lowered to 90 mg/kg.
- Both levocetirizine and S-cetirizine induced emesis at 45 and 135 mg/kg.
- Target organ was the gastrointestinal tract.
- Both levocetirizine and S-cetirizine have a similar toxicity profile with levocetirizine being more toxic.

Study no.: No. RRLE95C004 (TX002)
Conducting laboratory and location: UCB S.A.Pharma Sector, R&D Dept. of Product Safety and Metabolism, Belgium
Date of study initiation: 11/4/91
GLP compliance: Yes.
QA report: yes (X) no ( )
Drug, Batch #, and % purity: levocetirizine, # D005, Not stated.

Methods

Doses: 0 (capsule) levocetirizine, 15, 45, 135 mg/kg; due to a moribund condition, the 135 mg/kg dose was lowered to 90 mg/kg from day 8 of treatment.
S-cetirizine, 15, 45, 135 mg/kg
Species/strain: Beagle dogs.
Number/sex/group or time point (main study): 3.

Route, formulation, volume: Oral, capsule.
Satellite groups used for toxicokinetics or recovery: None.
Age: 20-23 weeks.
Weight: Males, 7.9-8.5; females, 7.9-8.3 kg.
Sampling times: 0, 1.5, 3, 6, 9 and 24 hr post dose.
Unique study design or methodology (if any): None.

Observations and times:
Mortality: Daily.
Clinical signs: Daily.
Body weights: Day 1 and weekly.
Food consumption: Daily.
Ophthalmoscopy: Prior to start of study and during week 4.
EKG: Prior to start of study and during week 4. Recording made prior to and 1 and 4 hr post dosing.
Hematology: Prior to start of study and during week 4.
Clinical chemistry: Prior to start of study and during week 4.
Urinalysis: Prior to start of study and during week 4. At necropsy, contents of the urinary bladder were collected for analysis.
Toxicokinetics: Days 1 and 23. The lloq was 0.3 ug/ml in the plasma and 5 ug/ml in the urine. On days 1 and 23, contents of 24 hr urines were collected for analysis.
Gross pathology: Week 4.
Organ weights: Organs weighed are listed in the histopath table.
Liver: A section was taken for analysis for microsomal protein, cytochrome P-450 levels, aniline 4-hydroxylase, ethylmorphine N-demethylase, p-nitroanisole, O-demethylase, 7-ethoxyresorufin O-demethylase and p-nitrophenol-UDPGT activities and liver weight.
Histopathology: Tissues listed in the histopath table from all groups were examined.
Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

Results

Mortality: Levocetirizine, HD, 1 male (day 5 killed in a moribund condition); animal showed reduced activity, hypersalivation, abnormal gait walking, tremors and muscular contractions, hypothermia, nausea, traceitis and fecal impaction; Neutrophils, and fibrinogen , alkaline phosphatase, glutamyltransferase, creatine phosphokinase and urea were elevated.
HD, 2 females (Days 8 and 9 the animals were killed in a moribund condition); findings were similar to the male that was killed. Both animals showed fecal impaction; one animal showed hepatocellular vacuolation and ileal ulceration and the other animal showed moderate tracheitis with focal ulceration.

Clinical signs: Male and female:
Levocetirizine: Emesis (% incidence in animals days) LD (3.3%), MD (11.8%), and HD (21.2%), HD, tremors, hypersalivation, nausea and instability.
S-cetirizine: Emesis (% incidence in animals days) LD (2.9%), MD (15.6%), and HD (38.8%): HD, hypersalivation.

Body weight gained: Levocetirizine and S-ceterizine: No change.
Food consumption: Levocetirizine and S-ceterizine: No change.
EKG: Levocetirizine and S-ceterizine: No change.
Ophthalmoscopy: Levocetirizine and S-ceterizine: No change.
Hematology: Levocetirizine and S-ceterizine: No change.
Clinical chemistry: Levocetirizine and S-ceterizine: No change.
Urinalysis: Volume: HD male, levocetirizine, +50%; S-cetirizine, +84%.
This was not levocetirizine related since increased urine volume was not seen in the 13-week oral toxicity study. In NDA 19-835, increased urine volume was not seen in the 1-year oral study.
Toxicokinetics and Urinalysis: Data for the males and females were pooled since the sponsor indicated that there was no sex difference. In the table below excerpted from the submission, the Cmax only increased in the HD S-cetirizine group resulting in accumulation. Both levocetirizine and S-cetirizine were significantly excreted in the urine (Ae) unchanged which increased upon repeated administration.

		DOSE (mg/kg/day)		
Parameter	Time	15	45	135/90*
ucb 28556				
Cmax (µg/ml)	D1	33.4 ± 8.2	83.0 ± 12.2	112.7 ± 38.3
	D23	39.3 ± 9.7	100.1 ± 9.6	159.9 ± 19.1
AUC (µg.h/ml)	D1	297 ± 43	856 ± 240	1432 ± 563
	D23	493 ± 41	1503 ± 155	2413 ± 445
Ae (% of dose)	D1	21.2 ± 5.9	19.6 ± 4.6	11.1 ± 6.4
	D23	39.4 ± 4.2	38.9 ± 7.0	33.4 ± 2.7
ucb 28557				
Cmax (µg/ml)	D1	27.7 ± 6.4	61.7 ± 10.0	67.3 ± 36.0
	D23	31.8 ± 5.2	72.7 ± 17.3	175.0 ± 39.1
AUC (µg.h/ml)	D1	277 ± 29	826 ± 141	1108 ± 698
	D23	429 ± 40	1062 ± 184	2941 ± 930
Ae (% of dose)	D1	28.5 ± 2.6	27.9 ± 1.8	11.3 ± 5.1
	D23	45.6 ± 5.1	42.3 ± 2.9	34.4 ± 8.6

* The high dose was reduced to 90 mg/kg/day for ucb 28556 from Day 8 onwards.

Bile levels of levocetirizine and S-cetirizine are shown in the following table excerpted from the submission. The presence of the levocetirizine and S-cetirizine in the bile indicates that fecal excretion for both compounds is partially or wholly by way of the biliary system.

Daily dose (mg/kg)		ucb 28556 (µg/ml)	ucb 28557 (µg/ml)
15	Males Females	224 204	243 383
45	Males Females	888 903	1092 1107
135/90	Males Females	1538 1344	2461 3079

Gross pathology: None in the survivors. In the killed male, there was fecal impaction; in the 2 animals that died, both showed fecal impaction.

Organ weights: No effect.

Liver: No increase in microsomal enzymes.

Histopathology: None in the surviving animals. In the killed male, there was traceitis; in the 2 female animals that died, one showed hepatocellular vacuolation, ileal ulceration, and the other dog showed ileal ulceration and tracheitis.

Study title: **4-Week oral toxicity in dogs of Levocetirizine, and S-cetirizine compared with cetirizine with a 4-week recovery.**

Key study findings:

Levocetirizine, S-cetirizine and Cetirizine

- Both levocetirizine and cetirizine were toxic at 135 mg/kg requiring the dose to be lowered to 90 mg/kg.
- S-cetirizine was lethal towards the end of the study.
- Emesis occurred at all doses with all three compounds.
- Target organs were the gastrointestinal tract, thymus, bone marrow and lungs.
- The toxicity profile of 135/90 mg/kg of levocetirizine, S-cetirizine and cetirizine were similar.

Study no.: No. RRLE99J1401 (TX008)
Conducting laboratory and location: UCB S.A.Pharma Sector, R&D Dept. of Product Safety and Metabolism, Belgium
Date of study initiation: 9/27/93.
GLP compliance: Yes.
QA report: yes (X) no ( )
Drugs, Batch #, and % purity: levocetirizine, #DO11, 99.8% cetirizine, # 2080, 99.53%; S-cetirizine,

Methods

Doses: 0 (capsule) levocetirizine, 33.75 and 67.5 and 135/90 mg/kg; S-cetirizine, 33.75 and 67.5 and 135 mg/kg; cetirizine, 135/90 mg/kg. The HD of levocetirizine and the dose of cetirizine were lowered to 90 mg/kg on day 11 for the females and on day 18 for the males due to severe toxicity. Dosing was halted 2-5 days prior to administering the 90 mg/kg dose.
Species/strain: Beagle dogs.
Number/sex/group or time point (main study): 3.
Route, formulation, volume: Oral, capsule.
Satellite groups used for the 4-week recovery: C and HD, levocetirizine, S-cetirizine and cetirizine, 1 additional animal/sex.
Age: 10-12 months.
Weight: Males, 8.6-13.2 kg; females, 8.0-13.4 kg.
Sampling times: 0, 0.75, 1.5, 3, 6, 9 and 24 hr post dose.
Unique study design or methodology (if any): None.

Observations and times:

Mortality: Daily.
Clinical signs: Daily.
Body weights: Day 0 and weekly.
Food consumption: Daily.
Ophthalmoscopy: Prior to initiating dosing ,week 4 and at the end of the recovery period.
EKG: Prior to initiating dosing, Day 24, before dosing and 1.5 hr post dosing (Tmax) and once weekly during the recovery period.
Hematology, Clinical chemistry: Prior to initiating dosing, and during week 4 and during the recovery period.
Urinalysis: Day 1, day 18 (females) and day 29 (males) and at sacrifice.
Toxicokinetics: Day 1 and during week 3/4.
Bile: Collected at necropsy and analyzed.
Gross pathology:
Organ weights: Organs weighed are listed in the histopath table.
Liver: A section was taken for analysis for microsomal protein, cytochrome P-450 levels and for aniline 4-hydroxylase, ethylmorphine N-demethylase, p-nitroanisole O-demethylase and 7-ethoxyresorufin O-demethylase activities.
Histopathology: Tissues listed in the histopath table from all groups were examined.

Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )

Results

Mortality:
Levocetirizine: HD, 2 females were killed in a moribund condition on days 9 and 17, respectively. Both animals showed emesis, tremors, hypersalivation, decreased muscle tone, hypothermia, tachycardia, stability problems, coughing, decreased body weight and low food consumption. Both animals showed elevated clinical enzymes.

S-cetirizine: MD, 1 female. From day 15, there was emesis, coughing, hypersalivation, and discharge from the eyes, lying on its side, tachycardia and tremors; there was increased lung weight due to inhalation of vomitus. Histopathology revealed inhalation bronchopneumonia due to aspiration.
HD, 2 females were moribund and were killed on day 26. These animals manifested tremors, abnormal gait, liquid feces, hypersalivation, reduced activity, tachycardia, decreased muscle tone and hypothermia.
Cetirizine: 1 female dog was killed in a moribund condition on day 9. There was high incidence of emesis, hypersalivation, tremors, fecal impaction and ocular discharge.

Clinical signs: Levocetirizine; LD, emesis.
MD, emesis, hypersalivation, tremors, and abnormal gait.
HD, hypersalivation, emesis, soft feces, tremors, coughing, stability problems, circling movements and decreased muscle tone. All these signs were absent at the end of the recovery period.
S-cetirizine: LD, emesis.
MD, emesis.
HD, hypersalivation, emesis, liquid feces, tremors, abnormal gait, ocular discharge, coughing, stability problems, circling movements and decreased muscle tone. All these signs were absent at the end of the recovery period.
Cetirizine: Abnormal gait waddling, tremors, hypersalivation, decreased muscle tone, nausea and emesis. These signs disappeared during the recovery period.

Body weight gained: No effect in the levocetirizine, S-cetirizine and cetirizine animals.

Food consumption: No effect in the levocetirizine, S-cetirizine and cetirizine animals.

Ophthalmoscopy: No effect.

EKG: QTC: levocetirizine, HD +15%; reversible. This was not confirmed in another 4-week oral toxicity study and is not treatment related.

Hematology: Eosinophils, levocetirizine, HD, female, +93%.

Clinical chemistry: No effect.

Urinalysis: No effect.

Toxicokinetics: Data for the males and females were pooled since the sponsor indicated that there was no sex difference. The following table was excerpted from the submission.

At the HD, levocetirizine (UCB28556) and S-cetirizine (UCB28557) and not cetirizine (ucb P071) showed accumulation, and all three compounds showed increased urinary excretion of the respective parent compound with multiple dosing.

Pharmacokinetic parameters

Test substance		ucb 28556			ucb P071
Dose (mg/kg/day)		33.75 (n=6)	67.5 (n=6)	135/90 (n=6 to 8)	135/90 (n=7 to 8)
C_{max} *	Day 1	64±16	102±29	124±46	73±20
	Day 18-29	101±27	180±52	208±22	108±19
T_{max}**	Day 1	1.9±0.9	1.8±0.6	2.3±1.7	2.8±1.5
	Day 18-29	2.4±1.0	2.8±0.6	3.0±1.6	2.4±0.8
AUC***	Day 1	629±74	1367±458	1479±833	1028±464
	Day 18-29	1318±294	2723±796	3065±344	1567±555
Test substance		ucb 28557			ucb P071
Dose (mg/kg/day)		33.75 (n=6)	67.5 (n=5 to 6)	135 (n=8)	135/90 (n=7 to 8)
C_{max}*	Day 1	48±23	65±27	113±57	57±15
	Day 18-29	68±14	168±27	235±61	89±18
T_{max}**	Day 1	1.8±0.6	2.0±0.8	2.8±1.5	3.2±1.9
	Day 18-29	2.3±0.8	2.4±0.8	6.2±7.4	3.0±1.5
AUC***	Day 1	564±286	805±486	1728±1007	879±356
	Day 18-29	963±152	2400±124	4345±1761	1313±491

*: C_{max} in µg/ml; **: T_{max} in hour; ***: AUC in µg.h/ml

Urinary excretion (% dose)

Test substance	ucb 28556			ucb P071
Dose (mg/kg/day)	33.75 (n=6 to 8)	67.5 (n=6 to 8)	135/90 (n=6 to 8)	135/90 (n=7)
Day 1	17.2±6.3	25.9±6.6	9.0±3.5	9.9±4.4
Day 18-29	41.9±13.4	36.1±6.8	36.1±10.9	30.8±7.4
Test substance	ucb 28557			ucb P071
Dose (mg/kg/day)	33.75 (n=5 to 8)	67.5 (n=5 to 8)	135 (n=5 to 8)	135/90 (n=7)
Day 1	25.0±14.4	14.5±6.9	14.0±5.5	11.5±4.7
Day 18-29	34.2±9.2	36.2±9.1	31.0±12.0	33.5±7.9

* Cmax in ug.ml; ** Tmax in hours; ***AUC in ug.hr/ml

Gross pathology: Fecal impaction:
Levocetirizine: Males, C, 0/3; LD, 0/3; MD, 1/3; HD, 1/3
Females, C, 0/3; LD, 0/3; MD, 1/3; HD, 1/3
Cetirizine: Males, 0/3; females, 2/2
S-cetirizine: None.
Recovery groups showed no fecal impaction.

Organ weights: No effect.

Liver Enzymes: No effect.

Histopathology (surviving dogs): Trachea: Mucosal atrophy:
Males, C, 0/3; levocetirizine, MD, 2/3; HD, 2/3; cetirizine, 0/3; S-cetirizine, HD, 2/3

Trachea: Loss of goblet cells:
Males, C, 0/3; Levocetirizine, MD, 2/3: HD, 2/3; S-cetirizine, HD, 3/3

Histological changes seen the moribund/killed female HD animals are summarized below:

Levocetirizine

Female No. 1:
Immature erythroid and myeloid bone marrow cells,
Multifocal granulocytic inflammation of the trachea,
Eosinophilic material with multifocal inflammation and macrophage accumulation in the alveoli of lungs,
Thymic atrophy.

Female No. 2:
Immature erythroid and myeloid bone marrow cells,
Neutrophilic infiltration in the colon and rectum,
Mucosal atrophy and loss of goblet cells in the trachea,
Alveolar macrophage accumulation and focal fibrosis in the lungs.

Cetirizine

Female:
Immature erythroid and myeloid bone marrow cells,
Diffuse granulocytic inflammation, loss of goblet cells in the trachea,
Macrophage accumulation and focal fibrosis in the lungs,
Thymic atrophy.

S-Cetirizine

Female No. 1:
Immature erythroid and myeloid bone marrow cells,
Multifocal granulocytic inflammation, loss of goblet cells and mucosal hyperplasia/disorganization in the trachea,
Multifocal congestion with focal alveolar hemorrhage in the lungs,
Thymic atrophy.

Female No. 2:
Mucosal erosion with villus atrophy in the ileum and with loss of goblet cells in the rectum,
Bone marrow and thymic atrophy,
Multifocal granulocytic inflammation, loss of goblet cells and mucosal hyperplasia/disorganization in the trachea,
Focal macrophage accumulation and eosinophilic material in the lung.

In another 4-week oral toxicity study in dogs, at oral doses of 15, 45 and 135/90 mg/kg for levocetirizine and S-cetirizine, tracheal mucosal atrophy and loss of goblet cells were not seen at the same HD of levocetirizine used in this study. These animals showed traceitis, hepatocellular vacuolation and ileal ulceration. Further, loss of goblet cells was not seen at 135 mg/kg, orally of cetirizine (NDA 19-835).

Study title: **13-Week oral toxicity in dogs.**

Key study findings:

- Emesis occurred at the HD in males while in females the incidence was increased at all oral doses.
- The target organ was the gastrointestinal tract.

Study no.: No.RRLE92G1003 (UCB413).
Conducting laboratory and location: (b) (4)
Date of study initiation: 12/10/91
GLP compliance: Yes.
QA report: yes (X) no ( )
Drug, Batch #, and % purity: Levocetirizine, # D006, 100.3%.

Methods

Doses: 0 (capsule) Levocetirizine, 8, 25, 75 mg/kg .
Species/strain: Beagle dogs.
Number/sex/group or time point (main study): 4.
Route, formulation, volume: Oral, capsule.
Satellite groups used for toxicokinetics or recovery: None.
Age: 20-23 weeks.
Weight: Males/ females, 7.2-10.5 kg.
Sampling times: 0, 1.5, 3, 6, 9, 12 and 24 hr post dose.
Unique study design or methodology (if any): None.

Observations and times:
Mortality: Daily.
Clinical signs: Daily.
Body weights: Day 0 and weekly.
Food consumption: Daily.
Ophthalmoscopy: Prior to and during week 13.
EKG: Prior to and during weeks 6 and 13. Determination was made 3 hr post dosing.
Hematology: Weeks -2, 6 and 13.
Clinical chemistry: Weeks -3, 6 and 13.
Urinalysis: Weeks -1, 6 and 12.
Toxicokinetics: Day 1 and during week 13. The lloq was 0.3 ug/ml in the plasma and 5 ug/ml in the urine. Bile was analyzed at the time of sacrifice.
Gross pathology: Week 13.
Organ weights: Organs weighed are listed in the histopath table.

Liver: Sections of the liver were stained for fat with Oil Red O and for glycogen with Schiff reagent.

Histopathology: Tissues listed in the histopath table from all groups were examined.
Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

Results

Mortality: None.
Clinical signs: Emesis; the incidence is summarized in the following table.

Group Dose, mg/kg, orally	% of the Possible Maximal Incidence of Emesis	
	Male	Female
C	<1	1
8	2	5
25	<1	8
75	10	6

Body weight gained: No effect.

Food consumption: No effect.

Ophthalmoscopy: No change.

EKG: Week 6, Heart rate, females, HD, +21%; Week 13, +27%. This was not seen in another 13-week oral toxicity studies and is not considered treatment related.

Hematology: Platelets, HD, females, +38%. This was not seen in another 13-week oral toxicity studies and is not considered treatment related.

Clinical chemistry: Cholesterol, HD, males, +17%. This was not seen in a second 13-week oral toxicity study and is not considered treatment related.

Urinalysis: This increase in total protein is not seen in a second 13-week oral toxicity study and is not considered treatment related.

Time Dose	Increase in Total Protein, P<0.05	
	Male	Female
Week 6 HD	+84%	+73%
Week 12 MD HD	- +73%	+43% +89%

Toxicokinetics: Data is the mean of the males and females. Accumulation occurred at the MD and HD. Levocetirizine has a long half life which may account for accumulation.

Parameter	**LD**		**MD**		**HD**	
	Day 1	**Week 13**	**Day 1**	**Week 13**	**Day 1**	**Week 13**
Cmax, ug/ml	16.9	22.0	38.9	78.6	101.3	167.1
AUC_{0-24hr} ug.hr/ml	114	191	308	808	923	2154
T1/2, hr	20.6		35.2		34.8	

Bile Excretion: The following table shows that levocetirizine is excreted in the feces by the biliary tract.

LD	**MD**	**HD**
63.0 ug/ml	319 ug/ml	1785 ug/ml

Urinary Excretion: Results are presented as % of the dose. Increased excretion of levocetirizine in the urine was maximally achieved by week 6.

Day/Week	**LD**	**MD**	**HD**
Day 1	13.1	14.6	16.1
Week 6	20.2	27.0	32.4
Week 13	20.8	27.9	32.1

Gross pathology: None.

Organ weight: Absolute spleen weight: Males, MD, +61%; HD, +67%. This was not confirmed in a second 13-week oral toxicity study and is not considered treatment related.

Liver: Stained for fat and glycogen: None present.
Histopathology: None.

Study title: **13-Week oral toxicity in dogs of levocetirizine compared with cetirizine**

Key study findings:

- Emesis was seen with levocetirizine and cetirizine.
- Cetirizine decreased body weight gained in males .
- Levocetirizine and cetirizine show comparable toxicity profiles.

Study no.: No. RRLE97F0201(TX282).
Conducting laboratory and location: (b) (4)
Date of study initiation: 6/5/96
GLP compliance: Yes.
QA report: yes (X) no ( )
Drugs, Batch #, and % purity: Levocetirizine, # 100, 99.3%, 99.97%; cetirizine, # C95365-2233, 99.65%

Methods

Doses: 0 (capsule) Levocetirizine, 37.5 and 75 mg/kg; cetirizine, 75 mg/kg.
Species/strain: Beagle dogs.
Number/sex/group or time point (main study): 4.
Route, formulation, volume: Oral, capsule.
Satellite groups used for toxicokinetics or recovery: None.
Age: 21-23 weeks.
Weight: Males, 7.5-10.4 kg; females, 6.9-10.2 kg.
Sampling times: 0, 1.5, 3, 6, 9, 12 and 24 hr post dose.
Unique study design or methodology (if any): None.

Observations and times:
Mortality: Daily.
Clinical signs: Daily.
Body weights: Day 0 and weekly.
Food consumption: Daily.
Ophthalmoscopy: Weeks -3 and 13.
EKG: Weeks -3, 6 and 13. Determination was made 3 hr post dosing.
Rectal temperature: Weeks, -1, 4, 8 and 12 prior to and 3 hr post dose.
Hematology: Weeks -3, 6 and 13.
Clinical chemistry: Weeks -3, 6 and 13.
Urinalysis: Weeks -3, 6 and 13.
Fecal examination for blood: Week 6.
Toxicokinetics: Day 1 and day 6 of week 13.
Gross pathology: Week 13.
Organ weights: Organs weighed are listed in the histopath table.
Liver: Sections of the liver was assayed for drug metabolizing enzymes.

Histopathology: Tissues listed in the histopath table from all groups were examined.
Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )

Results

Mortality: None.

Clinical signs: Emesis; the incidence is summarized in the following table. Both compounds produced emesis. Levocetirizine treated females show a dose related effect in comparison to males.

Group Dose, mg/kg, orally	% of the Possible Maximal Incidence of Emesis	
	Male	Female
C	0	<1
Cetirizine , 75	13	9
Levocetirizine , 37.5	7	3
75	4	10

Body weight gained: Cetirizine produced in males.
a 32% decrease in body weight.

Group Dose, mg/kg, orally	Body Weight Gained (kg), 0-13 weeks	
	Male	Female
C	+3.7	+3.0
Cetirizine , 75	+2.5 [a]	+2.4
Levocetirizine , 37.5	+3.3	+3.0
75	+3.2	+2.7

[a] $P<0.01$

Food consumption: No effect.

Ophthalmoscopy: No effect.

EKG: This increase in Qtc is not a treatment related effect since this was inconsistently seen in one of two 4-week toxicity studies and in another 13-week toxicity study with levocetirizine and in a 6- month study with cetirizine (NDA 19-835).

Group Dose, mg/kg, orally	Qtc, % Increase (P< 0.05)			
	Week 6		Week 13	
	Male	Female	Male	Female
Cetirizine , 75	0	7	0	7
Levocetirizine , 37.5	0	0	0	0
75	10	7	0	7

Rectal temperature: No effect.

Hematology: These findings were not seen in another 13-week oral toxicity study with levocetirizine and in a 6 month study with cetirizine (NDA 19-835) and are not considered treatment related.

Parameter	% Change in Week 13 (P<0.05)					
	LD		HD		Cetirizine	
	Male	Female	Male	Female	Male	Female
Hemoglobin	0	0	-11	0	0	0
Reticulocytes	0	0	0	0	-43	0
Lymphocytes	0	-23	0	-38	0	0

Clinical chemistry: These findings were not seen in another 13-week oral toxicity study with levocetirizine and in a 6 month study with cetirizine (NDA 19-835) are not considered treatment related.

Parameter	% Change in Week 13 (P<0.05)					
	LD		HD		Cetirizine	
	Male	Female	Male	Female	Male	Female
Potassium	0	0	0	+10	0	+12
Phosphorous	0	+14	0	+22	0	+22

Urinalysis: No effect.

Fecal examination for blood: None detected.

Toxicokinetics: Pooled data from both sexes were submitted since they were similar. The results are shown in the following table. At both doses, levocetirizine shows accumulation. Similarly, cetirizine as evidenced by its 2 enantiomers also show accumulation. Increased excretion of levocetirizine and the 2 enantiomers of cetirizine in the urine are maximally achieved by week 6.

Compound	Levocetirizine		Cetirizine	
Dose, mg/kg	37.5	75	75	
			Levocetirizine	S-Cetirizine
Cmax, ug/ml, Day 1	46.4	66.1	35.6	29.2
Week 13	68.1	132	55.2	50.6
AUC $_{0\text{-}24\ hr}$, ug.hr/ml				
Day 1	369	637	392	393
Week 13	828	1668	880	805
% of Dose in urine				
Day 1	11.1	19.0	14.2	18.5
Week 6	25.2	32.3	31.2	36.0
Week 13	24.1	25.0	31.3	37.1

Gross pathology: None.

Organ weights: Rel. Liver weight: Female, HD, +30% in relative weight.
Absolute Salivary gland weight: Female, LD, -17%; HD, -18%
These findings were not seen in another 13-week oral toxicity study and are not considered treatment related.

Liver: No effect on the following drug metabolizing enzymes, CYP1A, CYP2B, CYP2E, CYP3A and UDP glucuronyltransferases.

Bone marrow smears: No effect.

Histopathology: These liver findings presented in the following table were not seen with levocetirizine at the same dose in another 13-week oral toxicity study reviewed in this submission. In a 1-year study, no testes changes were seen with 60 mg/kg, orally of cetirizine (NDA 19-835).

Organ Observation	Incidence							
	Control		Cetirizine		Levocetirizine			
	0		75 mg/kg		37.7 mg/kg		75 mg/kg	
	M	F	M	Female	M	F	M	F
Liver								
Small aggregates in Kupffler cells	0/4	0/4	0/4	0/4	0/4	0/4	0/4	3/4
Inflammatory cells	1/4	0/4	0/4	4/4	2/4	3/4	1/4	2/4
Testes								
Reduced Spermatogenesis[a]	0/4	-	2/4	-	0/4	-	0/4	

Histopathology inventory

Study	TA0283 13 wk	TA0282 13 wk	UCB412 13 wk	UCB 413 13 wk	TX008 4 wk	TX001 4-week	ISO-P071 TX002 4 wk
Species	Rat	Dog	Rat	Dog	Dog	Rat	Dog
Adrenals	X*	X*	X*	X*	X*	X*	X*
Aorta	X	X		X	X		X
bone Marrow smear							
Bone (femur)	X	X	X	X		X	
Brain	X*	X*	X*	X*	X*	X*	X*
Cecum	X	X	X	X	X	X	X
Cervix	X		X				
Colon	X	X	X	X	X	X	X
Duodenum	X	X	X	X	X	X	X
Epididymis	X*	X*	X*	X*	X*		X*
Esophagus	X	X	X	X	X	X	X
Eye	X	X	X	X	X	X	X
Fallopian tube							
Gall bladder		X		X	X		X
Gross lesions	X	X	X	X	X		X
Harderian gland	X		X				
Head							
Heart	X*	X*	X*	X*	X*	X*	X*
Ileum	X	X	X	X	X	X	X
Injection site							
Jejunum	X	X	X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*	X*	X*
Lachrymal gland		X		X			
Larynx	X		X				
Liver	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X	X*
Lymph nodes cervical	X	X	X	X	X	X	X
Lymph nodes, Popliteal	X*		X*				
Lymph nodes mandibular		X		X			
Lymph nodes, mesenteric	X*	X	X*	X	X		X
Mammary Gland	X	X	X	X	X	X	X
Nasal cavity	X		X				
Optic nerves		X		X		X	
Ovaries	X*	X*	X*	X*	X*	X*	X*
Pancreas	X	X*	X	X*	X*	X	X*
Parathyroid	X	X	X	X	X		X
Peripheral nerve							
Pharynx	X		X				
Pituitary	X*	X*	X*	X*	X*	X*	X*
Prostate	X*	X*	X*	X*	X*	X	X*
Rectum	X	X	X	X	X		X

Salivary glands	X*	X*	X*	X*	X	X	X
Sciatic nerve	X	X	X	X	X	X	X
Seminal vesicles	X*		X*			X	
Skeletal muscle	X	X	X	X	X	X	X
Skin	X	X	X	X	X	X	X
Spinal cord	X	X	X	X	X	X	X
Spleen	X*	X*	X*	X*	X*	X*	X*
Sternum (marrow)	X	X	X	X	X		
Stomach	X	X	X	X	X	X	X
Testes	X*	X*	X*	X*	X*	X*	X*
Thymus	X*	X*	X*	X*	X*	X	X*
Thyroid	X*	X*	X*	X*	X*	X	X*
Tongue	X	X	X	X	X	X	
Trachea	X	X	X	X	X	X	X
Urinary bladder	X	X	X	X	X	X	X
Uterus	X*	X*	X*	X*	X*	X*	X*
Vagina	X	X	X	X	X		
Zymbal gland							

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology

Study title: **Reverse bacterial mutation assay.**

Key findings:

- Levocetirizine was not mutagenic in the Reverse bacterial mutation assay

Study no.: RRLE99K1101
Conducting laboratory and location: (b) (4)
Date of study initiation: 6/14/99
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, Batch # and % purity: levocetirizine, 506 and 100.36%.
Methods

Strains/species/cell line: Salmonella typhimurium TA1535, TA1537, TA98, TA100 and Escherichia coliWP2 *uvrA*

Doses used in definitive study: -S9:156.5, 312.5, 625, 1250, 2500 and 5000 ug/plate
+S9: 31.25, 62.5, 125, 250 and 500 and 1000 ug/plate.
Basis of dose selection: With Salmonella typhimurium TA100, concentrations of 0.1, 1, 10, 100, 1000 and 5000 ug/ml were tested in the presence and absence of S9 for toxicity. A very thin lawn was seen at 1000 and 5000 ug/ml in the absence of S9 and a thin lawn was observed at 5000 ug/ml in the presence of S9.

Vehicle: Ultra pure water for levocetirizine and control and dimethylsulfoxide for the positive controls except methyl methanesulfonate which was dissolved in ultra pure water.

S9: Livers from male Fisher 344 rats treated with Araclor 1254.

Positive controls:

Organism	With S9, Conc. (µg/plate)	Without S9, Conc. (µg/plate)
Salmonella typhimurium		
TA98	2-Aminoanthracene, 0.5	2-Nitrofluoorene, 1
TA100	2-Aminoanthracene, 0.5	Methyl methane sulfonate, 200 ug
TA1535	2-Aminoanthracene, 2	N-ethyl-nitro-N-nitrosoguanidine, 5 ug
TA 1537	2-Aminoanthracene, 2	9-Aminoacridine, 80
Escherichia coli WP2uvrA	2-Aminoanthracene, 20	N-ethyl-nitro-N-nitrosoguanidine, 2 ug

Incubation and sampling times: Preincubated for 20 min at 37◦ C followed by incubation at 37◦ C for 2 days.

Results

Study validity: The test was conducted in triplicate twice in the presence and absence of S9. The number of revertant cells was counted with a Biotran III automated counter with a sensitivity of counting cells ≥0.1 mm in cell diameter. For a significant mutagenic response, these criteria were met.

1. For S. typhimurium strains TA 1535, TA1537, and TA98 and for E. coli, there was at least a doubling of the mean current control; for S. typhimurium TA100, a 1.5 fold increase over the mean current control. If the mean colony count for the mean current control was less than 10, a value of 10 was assumed for assessment purposes; then a value of 20 was required for a positive response.
2. A dose related response was required. However, at the high dose levels, the dose response may be inverted due to toxicity to the bacteria, toxicity to the mutants and inhibition of the metabolizing enzymes where mutagens require metabolic activation by the liver.
3. A reproducible mutagenic effect.

Study outcome: Levocetirizine was not mutagenic in the presence and absence of metabolic activation. Thin or no lawns were seen at the high concentrations, and the positive controls produced a mutagenic response.

Reverse bacterial mutation assay

Key finding: Levocetirizine was inactive in the Reverse bacterial mutation assay.

Study no.: **No. RRLE92B1303**

Conducting laboratory and location: (b) (4)
Date of study initiation: 6/14/99
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, Batch # and % purity: levocetirizine, D005 and 99.2%-99.6%6%.

Methods

Strains/species/cell line: Salmonella typhimurium TA1535, TA1537,TA1538, TA98 and, TA100.

Doses used in definitive study: -S9 and +S9: 0, No solvent; 0, solvent 50, 150, 500, 1500 and 5000 ug/plate
Basis of dose selection: No toxicity was seen in the presence and absence of S9 at concentrations of 5, 50, 500 and 5000 ug/plate .
Vehicle: Ultra pure water for levocetirizine and control and dimethylsulfoxide for the positive controls except methyl methanesulfonate which was dissolved in ultra pure water.
Incubation period: 37 °C for 3 days.
S9: Livers from male Sprague-Dawley rats treated with Araclor 1254.

Positive controls:

Organism	With S9, Conc. (µg/plate)	Without S9, Conc. (µg/plate)
Salmonella typhimurium		
TA98	2-Aminoanthracene, 0.5	2-Nitrofluorene, 1
TA100	2-Aminoanthracene, 1	N-ethyl-nitro-N-nitrosoguanidine, 3 ug
TA1535	2-Aminoanthracene, 2	N-ethyl-nitro-N-nitrosoguanidine, 5
TA 1537	2-Aminoanthracene, 2	9-Aminoacridine, 80
TA1538	2-Aminoanthracene, 0.5	2-Nitrofluoorene, 2

Results

Study validity: The test was conducted in triplicate twice in the presence and absence of S9. The number of revertant cells was counted with a Biotran III automated counter. For a significant mutagenic response, these criteria were met.

There was at least a doubling of the mean current control in the presence or absence of S9 for each strain.

A dose related response was required. However, at the high dose levels, the dose response may be inverted due to toxicity to the bacteria, toxicity to the mutants and inhibition of the metabolizing enzymes where mutagens require metabolic activation by the liver.

A reproducible mutagenic effect.

Study outcome: Levocetirizine was not mutagenic in the presence and absence of metabolic activation. There was no toxicity as evidence by the presence of a complete background bacterial lawn.

Study Title: Micronucleus assay in mice, No. RRLE92F1501

Key findings

1. Levocetirizine was negative in the Mouse Micronucleus assay.

Study no.: RRLE92F1501
Conducting laboratory and location: (b) (4)

Date of study initiation: 2/18/92.
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: levocetirizine, D005, 99.6%

Methods

Strains/species/: Male and female (22-24 g), SPF CD-1 outbred mice of Swiss origin.
Doses: Preliminary toxicity evaluation (vehicle water:
Test 1: 50, 150, 450, 1350 mg/kg (2/sex/dose)
Test 2: 512,640, 800, 1000 mg/kg (2/sex/dose)
Definitive test: C (15 mice/sex), 800 mg/kg (20/sex)
Positive control: Mitomycin, 12 mg/kg, orally (5/sex/group); vehicle: 0.9% saline.
Route, volume: Oral, 20 ml/kg.

Basis of dose selection: In a preliminary toxicity studies, death occurred in 3/4 mice at 1350 mg/kg and 2/4 mice at 1000 mg/kg.

Observation Period: 2 days.

Following administration the animals were observed during the course of the study and weighed on days 1, 2 and 3. Five males and 5 females were sacrificed at 24, 48 and 72 hrs following oral administration. At the end of 72 hr the remaining animals were killed. The positive control animals were sacrificed 24 after administration. The bone marrows were removed, processed, stained with Giemsa and coded. From the bone marrow of each animal, 1000 polychromatic erythrocytes (PCE) were examined for the number of micronucleated polychromatic (MPCE). The ratio of polychromatic to normochromatic erythrocytes for each animal was determined by examining at least 1000 erythrocytes. Criteria: A positive response was a significant increase in the percent of MPCE compared to the vehicle control for at least one sampling time. In borderline cases, e.g. where the individual mean values fall outside the historical control range, further slide reading or testing may be necessary. A significant decrease in the ratio of polychromatic to normochromatic erythrocytes was indicative of bone marrow depression. A very large decrease in the ratio indicated cytotoxicity.

Results

From the preliminary oral toxicity studies, levocetirizine was lethal at 1000 and 1350 mg/kg. The 800 mg/kg oral dose in the definitive study was an acceptable test dose. Levocetirizine at the three time points did not increase the incidence of micronucleated cells while there was a significant increase in the number of micronucleated cells with the positive control. Neither levocetirizine nor the positive control decreased the ratio of the polychromatic to normochromatic erythrocytes or increased the number of micronucleated cells per 1000 normochromatic erythrocytes.

Study outcome: Levocetirizine was not genotoxic in the Micronucleus test in mice.

Chromosome Aberration assay in human lymphocytes

Key findings:

- Levocetirizine was positive in the absence of S9 at a non-cytotoxic concentration, but it was not confirmed in a subsequent study (RRLE06B1736).
- Levocetirizine was negative in the presence of S9.

Study no.: **No.RRLE95K0202**

Volume and page #: NA.
Conducting laboratory and location: (b) (4)
Date of study initiation: 5/4/94.
GLP compliance: yes (X) no ( ).
QA reports: yes (X) no ( ).
Drug, Batch #, and % purity: D011, 99.8%.

Methods:

Strains/species/cell line: Human peripheral lymphocytes.
Dose selection criteria:
Basis of dose selection: Decrease in Mitotic Index
Range finding studies for the effect on the Mitotic Index in the 2 experiments are shown in the following tables excerpted from the report.
Stability: Not stated.
Metabolic activation system: Livers from rats pretreated with Aroclor.
Controls:
Vehicle: Purified water.
Negative controls: Purified water.
Positive controls: For -S9, 4-Nitroquinolone 1-oxide (NQO); for S9+, Cyclophosphamide
Comments: Vehicle for positive controls: Dimethylsulfoxide.
Exposure conditions:
Incubation (hr) + harvest times (hr): -S9, 20+0, 44+0.
+S9, 3+17, 3+41.
Colchicine (1µg/ml) was added at 1.5 hr prior to harvesting.

Study design:

Analysis:

No. of replicates: 2

Counting method: From slides with microscope. 100 cells from each duplicate culture were analyzed for structural aberration. Mitotic index was determined by analyzing 1000 cells per duplicate culture.

Criteria for a valid assay:

- The binomial dispersion test demonstrated acceptable heterogeneity.
- The proportion of cells with structural aberration (excluding gaps) in negative control culture fell within normal range.
- At least 160 cells out of the intended 200 cells were analyzable at each dose level.
- the positive controls induced statistical increase in the number of cells with structural aberration.

Criteria for positive results:

- A statistically increase in the proportion of cells with structural aberration (excluding gaps) increased at one or more concentrations.
- The proportion of cells with structural aberration at such doses at such doses exceeded the normal range.
- The results were confirmed in the second experiment.

Results

The results with the highest concentrations, exposure and harvest times, the percent change in the Mitotic Index at the highest concentrations and the increase and significance in the number of aberration cells are shown in the following table.

Conc., ug/ml	S9 + Presence 0 Absence	Exposure + Harvest Time, hr	% Change in Mitotic Index at HD	Mean No. of Aberration Cells		Significance + P<0.05 0 P>0.05
				C	HD	
116, 179, 275	0	20 +0	+63	1	1	0
275, 423, 650	+	3+17	-58	0	1	0
168, 240, 343	0	20 +0	+37	0	4	+
240, 343, 490	+	3+17	-64	1	3	0
240[a]	0	44+0	-60	2	2	0
490[a]	+	3+41	-7	1	3	0

[a] No positive control.

Study Outcome

Levocetirizine was positive in the absence of S9 at non-cytotoxic concentrations; it was not confirmed in a subsequent study. In the presence of S9, levocetirizine was negative.

Two other studies one with S9 and one without S9 were not valid since a positive control was not tested.

Chromosome Aberration assay in human lymphocytes

Key findings:

- In the presence of S9 Levocetirizine positive at a high cytotoxic concentration.
- In the absence of S9, levocetirizine was positive, but its activity was not confirmed.

Study no.: No.RRLE92F505.

Conducting laboratory and location: (b) (4)
Date of study initiation: 1/30/92.
GLP compliance: yes (X) no ( ).
QA reports: yes (X) no ( ).
Drug, Batch #, and % purity: D005, 99.6%.

Methods:

Strains/species/cell line: Human peripheral lymphocytes; cells were incubated with phytohaemagglutin to stimulate cells.
Dose selection criteria:
Basis of dose selection: Decrease in Mitotic Index

Test agent stability: Not stated.
Metabolic activation system: Livers from rats pretreated with Aroclor.

Controls:
Vehicle: Sterile distilled water.
Negative controls: Purified water.
Positive controls: -S9, Ethylmethanesulfonate, 750 ug/ml; S9+, Cyclophosphamide, 15 ug/ml.
Comments: Vehicle for positive controls: Ethylmethanesulfonate, Dimethylsulfoxide; cyclophosphamide, sterile distilled water
Exposure conditions:
Incubation (hr) + harvest times (hr):
First assay:-S9, 24 hr exposure.
+S9, 3 hr exposure + 21 hr recovery.
Second assay::-S9, 24 hr exposure.
-S9, 48 hr exposure.
+S9, 3 hr exposure + 21 hr recovery.

Colchicine (0.25µg/ml) was added at 2 hr prior to harvesting.

Study design:

Analysis:

No. of replicates: 2 and 2 trials were conducted.

Counting method: From slides with microscope. 100 metaphase cells from each duplicate culture were analyzed for structural aberration. Mitotic index was determined by analyzing 1000 cells per duplicate culture.

Criteria for a valid assay and for positive results: They were not described, but the study was conducted according to the OCED Guidelines for testing of Chemicals No. 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test" adopted 5/26/83 and the Department of Health Report on Health and Social Subjects No. 35. Guidelines for the testing of chemicals for mutagenicity (1989). The data were subjected to statistical analysis.

Results

The results with the highest concentrations, exposure and harvest times, the percent change in the Mitotic Index at the higher concentrations and the increase and significance in the number of aberration cells are shown in the following table.

Conc., ug/ml	S9 + Presence 0 Absence	Exposure + Harvest Time, hr	% Change in Mitotic Index Conc.	%	Mean No. of Aberration Cells C	T	Significance + P<0.05 0 P>0.05
78, 313,625	+	3+21	625	-75	2.8	14.5	+[b]
			313	+113	2.8	5.5	0
78, 400, 800	+	3+21	800	-60	1.8	14.0	+[c]
			400	+110	1.8	3.0	0
38, 150, 350	0	24+0	350	-47	3.3	9.0	+[c]
150, 350, 500	0	24 +0	500	-55	1.3	0.5	0
39, 156, 313[a]	0	48+0	313	-13	0.3	1.5	0

[a] No reference was tested.

[b] This activity was not confirmed when the slides were reexamined by (b) (4) Study No.: RRLE95L2807

This activity was confirmed when the slides were reexamined by (b) (4) Study No.: RRLE95L2807

Study Outcome

Levocetirizine in the presence of S9 was positive at a very high cytotoxic concentration and negative at non-cytotoxic concentrations. In the absence of S9, levocetirizine was positive, but its activity was not confirmed in a subsequent assay. One study was not valid since the study was conducted without a positive control.

Chromosome Aberration assay inhuman lymphocytes

Study No.: No.RRLE06B1736

Key Findings:

Levocetirizine was negative in a valid Human Lymphocyte Chromosomal Aberration Assay.

Conducting laboratory and location: (b) (4)
Date of study initiation: 4/30/92.
GLP compliance: yes (X) no ( ).
QA reports: yes (X) no ( ).
Drug, Batch #, and % purity: 05B201020, 99.8%.

Methods:

Strains/species/cell line: Human peripheral lymphocytes; cells were incubated with phytohaemagglutin to stimulate cells.
Dose selection criteria:
Basis of dose selection: Decrease in Mitotic Index

Test agent stability: Not stated.
Metabolic activation system: Livers from rats pretreated with Aroclor.
Controls:
Vehicle: Sterile distilled water.
Negative controls: Purified water.
Positive controls: For -S9, Ethylmethanesulfonate, 750 ug/ml;
S9+, Cyclophosphamide, 15 ug/ml.
Comments: Vehicle for positive controls: Ethylmethanesulfonate, dimethylsulfoxide, cyclophosphamide, sterile distilled water
Exposure conditions:
Incubation (hr) + harvest times (hr):
One assay:-S9, 20 hr exposure + 0 hr recovery
Two assays +S9, 3 hr exposure + 17 hr recovery.
One assays -S9, 3 hr exposure + 17 hr recovery.

Colchicine (0.25µg/ml) was added at 2 hr prior to harvesting.

Study design:
Analysis:
No. of replicates: 2 and 2 trials were conducted.
Counting method: From slides with microscope. 100 metaphase cells from each duplicate culture were analyzed for structural aberration. Mitotic index was determined by analyzing 1000 cells per duplicate culture.

Criteria for a valid assay and for positive results: They were not described, but the study was conducted according to the OCED Guidelines for testing of Chemicals No. 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test" adopted 5/26/83 and the Department of Health Report on Health and Social Subjects No. 35. Guidelines for the testing of chemicals for mutagenicity (1989). The data were subjected to statistical analysis.

Results

The results with the highest concentrations, exposure and harvest times, the percent change in the Mitotic Index at the highest concentrations and the increase and significance in the number of aberration cells are shown in the following table.
No increase in aberration cells were seen at the low and mid concentrations. Unless indicated the references were positive. This was a valid assay as the highest concentration produced > 50% decrease in Mitotic Index.

Conc., ug/ml	**S9 + Presence 0 Absence**	**Exposure + Harvest Time, hr**	**% Change in Mitotic Index at HD**	**Mean No. of Aberration Cells C HD**	**Significance + P<0.05 0 P>0.05**
600, 650, 700	0	3+17	-44	1 2	0
400, 550, 650	+	3+17	-47	3 2	0
300, 550,600, 650	0	20+0	-65	1 1	0
600, 650, 700	+	3+17	-57	2 2	0

Study Outcome

Levocetirizine was negative in the Human Lymphocyte Chromosomal Aberration Assay.

Chromosome Aberration assay in human lymphocytes

Key findings:

- In the presence of S9, levocetirizine was positive at an excessive cytotoxic concentration, but was negative at a lower acceptable concentration.
- In the absence of S9, the assay was invalid since the highest test concentration did not produce inhibition of the Mitotic Index.

Study no. No.RRLE92G1503

Conducting laboratory and location: (b) (4)
Date of study initiation: 4/30/92.

GLP compliance: yes (X) no ( ).
QA reports: yes (X) no ( ).
Drug, Batch #, and % purity: D008, 99.7%.

Methods:

Strains/species/cell line: Human peripheral lymphocytes from 3 females; cells were incubated with phytohaemagglutin to stimulate cells.
Dose selection criteria:
Basis of dose selection: Decrease in Mitotic Index

Test agent stability: Not stated.
Metabolic activation system: Livers from rats pretreated with Aroclor.
Controls:
Vehicle: Purified water.
Negative controls: Purified water.
Positive controls: For -S9, 4-nitroquinoline, 2.5 ug/ml;
S9+, Cyclophosphamide, 12.5ug/ml.
Comments: Vehicle for positive controls: Dimethylsulfoxide,
Exposure conditions:
Incubation (hr) + recovery times (hr):
-S9, 24r exposure + 0 hr recovery.
+S9, 3 hr exposure + 17 hr recovery.

Colchicine (1 μg/ml) was added at 2 hr prior to harvesting.

Study design:
Analysis:
No. of replicates: 2 and 2 trials were conducted.
Counting method: From slides with microscope. 100 metaphase cells from each duplicate culture were analyzed for structural aberration. Mitotic index was determined by analyzing 1000 cells per duplicate culture.

Criteria for a valid assay:

- The binomial dispersion test demonstrated acceptable heterogeneity.
- The proportion of cells with structural aberration (excluding gaps) in negative control culture fell within normal range.
- At least 160 cells out of the intended 200 cells were analyzable at each dose level.
- the positive controls induced statistical increase in the number of cells with structural aberration.

Criteria for positive results (The following criteria must be met):

- The proportion of cells with chromosomal aberration at one or more concentrations exceeds the normal range in both replicate cultures.
- A statistically significant increase in the proportion of cells with chromosomal aberrations (excluding gaps) occurs at these doses.

- A concentration-related trend in the proportion of cells with structural aberrations (excluding gaps).

Results

The results with the higher concentrations exposure and harvest times, and the percent change in the Mitotic Index, the increase and significance in the number of aberration cells is shown in the following table.

Conc., ug/ml	S9 + Presence 0 Absence	Exposure + Harvest Time, hr	% Change in Mitotic Index		Mean No. of Aberration Cells		Significance + P<0.05 0 P>0.05
			Conc. ug/ml	%	C	T	
78, 250, 350	0	20+0	350	+139	0.75	1.0	0
60,78, 313, 625	+	3+17	625	-73	1.5	8.5	+
			313	+113	1.5	1.5	0

Study Outcome

In the absence of S9, the assay was invalid since the highest test concentration did not produce inhibition of the Mitotic Index. In the presence of S9, levocetirizine was positive at an excessive cytotoxic concentration, but was negative at a lower acceptable concentration relative to the cytotoxic concentration.

Chromosome Aberration assay in human lymphocytes

Key findings:

- In the absence of S9, levocetirizine was not adequately tested due to a concentration that was not cytotoxic or did not have a positive control in the study.

- In the presence of S9, levocetirizine was negative. In subsequent studies, the results were invalid since the highest concentration was not cytotoxic or a positive control was not tested.

Study no. No.RRLE95K0203

Conducting laboratory and location: (b) (4)
Date of study initiation: 5/5/94.
GLP compliance: yes (X) no ( ).
QA reports: yes (X) no ( ).
Drug, Batch #, and % purity: D008, 99.7%.

Methods:

Strains/species/cell line: Human peripheral lymphocytes from 3 females; cells were incubated with phytohaemagglutin to stimulate cells.
Dose selection criteria:
Basis of dose selection: Decrease in Mitotic Index

Test agent stability: Not stated.
Metabolic activation system: Livers from rats pretreated with Aroclor.
Controls:
Vehicle: Purified water.
Negative controls: Purified water.
Positive controls: For -S9, 4-nitroquinoline, 1.25, 2.5 or 2.5 ug/ml;
S9+, Cyclophosphamide, 12.5 or 25ug/ml.
Comments: Vehicle for positive controls: Dimethylsulfoxide.

Exposure conditions:

Treatment: Incubation (hr) + recovery times (hr):

Pulse Treatment: +S9, +3 hr exposure + 17 hr recovery
+S9, 3 hr exposure + 41 hr recovery.

Continuous Treatment:-S9, 20 hr exposure + 0 hr recovery
-S9, 44 hr exposure + 0 hr recovery

Colchicine (1 μg/ml) was added at 1.5 hr prior to harvesting.

Study design:

Analysis:
No. of replicates: Duplicates or quadruplicates were conducted.
Counting method: From slides with microscope. 100 metaphase cells from each duplicate culture were analyzed for structural aberration. Mitotic index was determined by analyzing 1000 cells per duplicate culture.

Criteria for a valid assay:

- The binomial dispersion test demonstrated acceptable heterogeneity.
- The proportion of cells with structural aberration (excluding gaps) in negative control culture fell within normal range.
- At least 160 cells out of the intended 200 cells were analyzable at each dose level.
- the positive controls induced statistical increase in the number of cells with structural aberration.

Criteria for positive results (The following criteria must be met):

- A statistically significant increase in the proportion of cells with chromosomal aberrations (excluding gaps) occurs at one or more concentrations.
- The proportion of cells with chromosomal aberration at one or more concentrations exceeds the normal range in both replicate cultures.
- The results were confirmed in a second experiment.

Results:

The results with the highest concentrations, exposure and harvest times, the percent change in the Mitotic Index, the increase and significance in the number of aberration cells are shown in the following table.

Conc., ug/ml	S9 + Presence 0 Absence	Exposure + Harvest Time, hr	% Change in Mitotic Index at HD	Mean No. of Aberrant Cells C	HD	Significance + P<0.05 0 P>0.05
116,179, 275[a]	0	20 + 0	+147	1	2	0
275, 423, 650[a]	+	3 + 17	-32	1	4	0
117, 168, 240	0	20 + 0	+94	2	0	0
343, 490, 700	+	3 + 17	-55	1	2	0
240[b]	0	44+0	-65	5	6	0
700[b]	+	3+41	-35	1	6	+

[a] Donor was a female; otherwise the donors were males.
[b] No positive control was tested.

Study Outcome

In the absence of S9, levocetirizine was not adequately tested in 2 studies, since the highest test concentrations did not produce inhibition of the Mitotic Index. In the third test whereby a single concentration was tested, no positive control was included in the assay which invalidated the assay. In the presence of S9, levocetirizine was not adequately tested since the highest concentration was not adequately cytotoxic which invalidated the results. In the second assay, levocetirizine was negative. In the third assay, the results were unacceptable since no positive control was tested.

Human lymphocyte metaphase analysis

Key Findings

- This was an invalid assay since no positive controls were used in the test.

Study no. No. RRLE95G1101

Conducting laboratory and location: (b) (4)
Date of study initiation: 3/30/94.
GLP compliance: yes (X) no ().
QA reports: yes (X) no ( ).
Drug, Batch #, and % purity: D008, 99.7% D006, and D005, 99.6%.

This study was conducted to compare the activity of Batches, D005, D006 and D008 in the Chromosomal Aberration Assay. The results were invalid since no positive controls were tested in the study.

Study outcome

This was an invalid assay since no positive controls were conducted in the test.

Mouse lymphoma test in mice

Key findings: Levocetirizine was inactive in the Mouse lymphoma assay.

Study no.: RRLE9K1102
Conducting laboratory and location: (b) (4)
Date of study initiation: 6/14/99
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Batch No. 506, 100.36%

Methods

Strains/species/cell line: Mouse Lymphoma L5178Y $TK^{+/-}$ cells.

Doses used in definitive study:
-S9
4 hr exposure, 50, 100,150, 200, 250, 300, 350 and 400 ug/ml
24 hr exposure, 50, 100,150, 200, 250, 300, 350 and 400 ug/ml

+S9
4 hr exposure, 12.5 25, 50, 100,150, 200, 250 and 300 ug/ml
4 hr exposure, 50, 100,150, 200, 250, 300, 350 and 400 ug/ml
Basis of dose selection: Decrease in Survival.

Negative controls: Solvent, water.
Positive controls: -S9: 4 hr, ethyl methanesulphonate (large colony inducer), 250 ug/ml + methyl methanesulphonate (small colony inducer) 15 ug/ml
24 hr, ethyl methanesulphonate, 150 ug/ml+ methyl methanesulphonate 5 ug/ml

+S9: 4 hr, 3-methylcholanthrene (large and small colony inducer)

2.5 ug/ml
Solvents: DMSO for ethyl methanesulphonate and
3-methylcholanthrene
Water for methyl methanesulphonate

S9 Mix: Prepared from livers of male Fisher rats treated with Aroclor 1254.

Incubation and sampling times: 4 or 24 hr and 48 hr for expression.

Study validity: Tests were conducted in duplicate cell cultures in the absence and presence of S9 except for the control which was conducted in quadruplicate. The cells in tubes were incubated at 37°C in a rotating drum for 4 or 24 hrs. Cell density was adjusted to $3x10^5$cells/ml. At the end of 24 hr, cells were sampled to determine survival. After the 48 hr expression time, cloning efficiency and mutant selection were determined; for cloning efficiency, two-96 well dishes were filled with 200 ul cell culture giving an estimate of 1.6 cell per well. The cloning efficiency were determined after incubation for 9 days at 37°C For the mutant selection, trifluorothymidine was added after 9 days and after 3 additional days, counts were made of the number of large and small colonies using a dissecting microscope.

The assay is valid if the following criteria were met.

1. The highest concentration of test compound was limited by solubility or toxicity or is the maximum practical concentration, i.e., 5000 ug/ml.
2. The positive and vehicle control data were within or close to the laboratory's historical control data.
3. There was an absence of confounding technical problems.

If the test substance is toxic, the highest concentration tested should be at 20% survival.

The following criteria were applied for a positive finding.

1. If one or more concentrations were statistically significant, and there was a linear trend. In the absence of a trend, there was mitigating evidence to account for this response.
2. If one concentration was significant since there was evidence that only one concentration was expected to be active, e.g. step toxicity curve. For this example, the test should be repeated using narrowing concentrations to produce toxicity at more than one concentration.

3. If the test substance was positive in 2 out of 2 experiments with the same activation condition. Test substances that gave a negative response in the standard exposure in the absence of S9 but gave a positive response in the extended exposure. This would require repeating the extended exposure for confirmation.

Results

The following table shows the % survival at the concentrations used in the definitive assay. No increase in aberration cells were seen in the studies that had low and mid concentrations; the references were positive.

Concentration ug/ml	Survival (%) Relative to Control at different Incubation Times (hr)			
	4 Hours, -S9	24 Hours, -S9	4 Hours, +S9	4 Hours, +S9
12.5	-	-	106	-
25	-	-	101	-
50	94	76	83	88
100	89	54	54	64
150	97	36	35	47
200	57	19	27	31
250	70	8	22	27
300	50	5 toxic	11 toxic	13
350	36	-	-	7 toxic
400	18 toxic	-	-	2 toxic

In all 4 assays, levocetirizine was negative at the concentrations tested.

Study outcome: Levocetirizine was not mutagenic in the Mouse lymphoma assay. This assay was valid.

Mouse lymphoma test in mice

Key findings: Levocetirizine was negative in the Mouse Lymphoma assay.

Study no.: RRLE92D0804
Conducting laboratory and location: (b) (4)
Date of study initiation: 1/22/92
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Batch No. D005, 99.2%

Doses used in definitive study:
-S9
3 hr exposure, 50, 150, 250 and 300 ug/ml
3 hr exposure, 50, 250, 300, 325 and 350 ug/ml
+S9
3 hr exposure, 25, 200, 250 and 300 ug/ml
3 hr exposure, 50, 250, 300 and 350 ug/ml

Basis of dose selection: Growth Suppression

Negative controls: Solvent, water.
Positive controls: -S9: 3 hr, ethyl methanesulphonate (large colony inducer), 500 ug/ml
+S9: 3 hr, 3-methylcholanthrene, 2.5 ug/ml

Solvents: Ethyl methanesulphonate, water
3-methylcholanthrene, DMSO

S9 Mix: Prepared from livers of male Fisher rats treated with Aroclor 1254.

Incubation and sampling times: 3 hr and 11-12 days for expression.

Study validity: Tests were conducted in duplicate cell cultures in the absence and presence of S9 except for the control which was conducted in quadruplicate. The cells in tubes were incubated at 37°C in a rotating drum for 3 hours. Cell density was adjusted to $2x10^5$cells/ml. At the end of 24 hr, cells were sampled to determine survival. After the 48 hr expression time, viability and mutant frequency were determined; viability was assessed by plating 200 cells in a cloning medium. Three plates were prepared for each concentration. Mutant frequency was determined by plating 10^6 cells in a selective medium and then placed in a humidifier incubator at 37°C. Following this, the plates were incubated for 11-12 days and the large and small colonies were counted with an Optomax V image analyzer. The assay was conducted twice.

The following criteria were applied for a positive finding.

At least a two-fold increase in mutant frequency in treated cultures relative to concurrent controls.

A significant increase in mutant frequency.
A dose related effect in at least two concentrations.
Demonstration of reproducibility in any increase in mutant frequency.
The increase in frequency must lie outside the historical control range

Results

In following table shows the % survival at the concentrations used in the definitive assay. There was no increase in the number of colonies.

Concentration ug/ml	**Survival (%) Relative to Control at different Incubation Times (hr)**			
	3 Hours, -S9	**3 Hours, -S9**	**3 Hours, +S9**	**3 Hours, +S9**
25	-	-	111	-
50	83	91	-	94

100	-	-	-	-
150	70	-	-	-
200	-	-	52	-
250	68	56	43	53
300	47	36	40	42
325	-	25	-	-
350	-	15	-	19

Study outcome: Levocetirizine did not increase the number of mutant colonies at the concentrations tested in the Mouse Lymphoma Assay. The reference compounds were positive. This was an acceptable assay.

Carcinogenicity: None submitted.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early developmental studies with cetirizine in rats, No. ARLE00C1001

Key Study Findings

- Cetirizine at oral doses up to 200 mg/kg did not affect fertility in males and females and early fetal development.

Groups of 22-30 Male (163-196 g) and female (191-224 g) rats received 5, 30 and 200 mg/kg orally of cetirizine. Males were administered daily for 63 days before mating and through the mating period until the day before necropsy, and females were administered daily for 14 days before mating and through the mating period until 7 days of gestation. Distilled water was the vehicle, and the volume administered was 5 ml/kg. The presence of a vaginal plug was day 0 of gestation.

Males
Semen was collected from the tail end of the epididymis after copulation; the sperm, the survival index, survival rate, morphology, and count were determined.

Females
They were killed on day 20 and necropsied, determining success or failure of gestation and the number of corpus lutea, implantation loss, live and dead fetuses and, placental weight.

Fetuses
Live fetuses were weighed, examined externally and sexed; one third were processed to

examine the morphology of the internal organs. The remaining fetuses were processed to examine the bony parts.

Results

Males

Mortality: 7/23 HD rats died. They showed abnormal respiratory sounds, salivation nervousness, gasping and piloerection.
Clinical signs**:** abnormal respiratory sounds, salivation nervousness, gasping, piloerection and hypothermia.

Body weight gained: HD, -18%.

Gross necropsy: HD dead animals: Seminal vesicle atrophy, accentuation of the lobular pattern of the liver and an enlarged liver.
HD survivors: accentuation of the lobular pattern of the liver, enlarged liver.

Sperm: Motility index, Survival rate, number of sperm, malformations: No change from control.

Females

Mortality/Moribund: 10/30 HD rats. They showed abnormal respiratory sounds, hypothermia, abdominal distention, gasping, and piloerection.

Clinical signs**:** abnormal respiratory sounds, gasping and piloerection.

Body weight gained during gestation: No change from control.

Food consumption during gestation: No change from control.
Gross necropsy: HD dead animals: Incomplete lung involution and congestion, retention of gas in the GI tract, small spleen and enlarged adrenals.
HD survivors: None.

Estrus cycle: HD, 25% increased**.**

Pregnancies: No change from control.

Corpora lutea, implants, Implant index, live fetuses, sex ratio, fetal weight, placental weight, no. of dead fetuses: No change from control. **Fetus**

External anomalies, skeletal, visceral anomalies, skeletal variations and ossifications: No change from control.

Study Outcome citirizine did not affect fertility and early fetal development in rats.

Embryofetal development

Study title: **The effect on embryofetal development in rats from oral administration of levocetirizine and cetirizine**

Key study findings:

- No embryofetal abnormalities were observed in pregnant rats at doses of 50, 100 and 200 mg/kg, orally of levocetirizine and at an oral dose of 200 mg/kg of cetirizine.

Study no.: No. RRLE93F3001
Volume #, and page #: NA
Conducting laboratory and location: (b) (4).
Date of study initiation: 8/31/92
GLP compliance: Yes.
QA reports: yes ( ) no ( )
Drug, lot #, and % purity: Levocetirizine D009, 99.4%; cetirizine. 2049, 101.67%

Methods

Oral Doses: Levocetirizine: 50 (LD), 100 (MD) and 200 (HD) mg/kg; cetirizine, 200 mg/kg.
Species/strain: Eight-10 week old male and female (Crl:CD(SD) BR VAF (Plus strain) rats.
Number/sex/group: 25.
Route, formulation, volume: Oral, distilled deioniozed water, 10 ml/kg.
Satellite groups used for toxicokinetics: 4 females/group.
Study design: Each female was time-mated with males prior to being sent by the supplier. The day of mating as judged by sperm in the vaginal smear or by the presence of a vaginal plug was considered day 0 of pregnancy. Females weighing between 184 and 214 g were randomized into groups of 15.Daily treatment was given by gavage from day 6 to day 15 of gestation.

Parameters and endpoints evaluated:

Dams:

Clinical signs: Daily. Animals that died, showing signs of ill health or killed for humane reasons were weighed and subjected to post mortem examination.
Food consumption: Day 3 of pregnancy.
Body weights: Initially (day 2 of pregnancy) and days 3, 6, 8, 10, 12, 14, 16, 18 and 20 (the day of sacrifice).
Toxicokinetics: On day 15 of gestastion, blood was taken from 2 rats 2 and 24 hr post dose.
At sacrifice, the following were examined:
The number of copora lutea.
The number and distribution of the live fetuses.
The number and distribution of embryofetal deaths.

The individual fetal weight from the litter weight was calculated.
The fetal abnormalities were determined.
The uteri or uterine horns were examined for implantation. Results were expressed as pre- or post-implantation loss as a percentage.

Embryofetal deaths were classified as early (placenta visible at determination) and late (placental and embryonic remnants visible at examination).

Fetus

They were examined externally, sexed and weighed.
Half were examined for visceral abnormalities and the other half were examined for skeletal abnormalities. Structural changes were classified as malformation, anomalies or variants.

Litter weight and mean fetal weight were calculated from individual fetal weight. Values were expressed based on within individual litters, and group values were derived as a mean of the individual litter values.

Results

Mortality: Levocetirizine: None; cetirizine, 2/25; one died on day 15, and the second animal were killed for humane reasons. Similar signs that were drug related were seen, i.e., salivation, wet coat and/or noisy or gasping respiration. In the second animal, the uterus contained 11 early embryonic deaths.

Non-Pregnancy: Levocetirizine: LD, 1/25; MD, 1/25.

Body Weight Gained ($P<0.05$): Day 16 of gestation, levocetirizine, HD, -18%; cetirizine, HD, -15%.

Food consumption: No change.

Litter data
Corpora lutea, pre- and post implantation loss, embryonic deaths, no. of live young, sex ratios and mean fetal weight: No change.

Fetus

Skeletal and Visceral malformations:
Based on incidence in total number of fetuses: None.
Based on incidence in number of litters affected: None.

Visceral and skeletal anomalies:
Based on incidence in total number of fetuses: None.
Based on incidence in number of litters affected: None.

Skeletal variants (based on % showing in fetuses: No change.

Toxicokinetics: Plasma levels at 2 and 24 hr on day 15 of gestation are shown in the following table excerpted from the report. The results are expressed in ug/ml.

Mean plasma concentrations (µg/ml) of ucb 28556 and ucb 28557 in the pregnant rat after daily oral administration of ucb 28556 or ucb P071 (Day 10 of treatment).

		ucb 28556			ucb P071	
Daily dose	Control	50 mg/kg	100 mg/kg	200 mg/kg	200 mg/kg ucb 28556	200 mg/kg ucb 28557
C2h	ND	31.4 ± 8.7	60.6 ± 19.5#	102.7 ± 21.1	43.2 ± 9.6#	21.0 ± 5.1
C24h	ND	0.01 ± 0.02	0.26 ± 0.35	0.72 ± 0.60	0.42 ± 0.41	0.11 ± 0.12

ND : none detected
: No statistically significant difference at C2h between ucb 28556 given as a single enantiomer (100 mg/kg) or as a racemate (n = 9)

At 200 mg/kg orally, the $C_{24\ hr}$ levels of levocetirizine were similar to the combined C_{24hr} levels of levocetirizine and S-cetirizine from the administration of 200 mg/kg of cetirizine in rats.

Study Outcome

Levocetirizine and cetirizine were not teratogenic in rats at comparable oral doses.

Study title: **The effect on embryofetal development in rabbits from oral administration of levocetirizine and cetirizine**

Key study findings:

- Levocetirizine at oral doses of 30, 60 and 120 mg/kg in rabbits did not produce malformations, visceral or skeletal anomalies and skeletal variants.
- Cetirizine at 120 mg/kg, orally produced a slight increased incidence of skeletal variants.

Study no.: No. RRLE93C3005
Volume #, and page #: NA
Conducting laboratory and location: (b) (4)
Date of study initiation: 8/24/92
GLP compliance: Yes.
QA reports: yes ( ) no ( )
Drug, lot #, and % purity: Levocetirizine D009, 99.4%; cetirizine. 2049, 101.67%

Methods

Oral Doses: Levocetirizine: 30 (LD), 60 (MD) and 120 (HD) mg/kg; cetirizine, 120 mg/kg
Species/strain: Sixteen-25 week old New Zeeland White pregnant rabbits (3.1-4.1 kg)
Number/sex/group: 16.
Route, formulation, volume: Oral, distilled deionized water, 5 ml/kg.
Satellite groups used for toxicokinetics: None.
Study design: Daily treatment was given by gavage from day 6 to day 18 of gestation and sacrificed on day 29 of gestation.
Parameters and endpoints evaluated:

Dams:
Clinical signs: Daily.
Body weights: Initially (day 0 of pregnancy) and days 3, 6, 8, 10, 14, 19, 23 and 29 (the day of sacrifice).
Toxicokinetics: Days 6 and 18, blood was taken from all animals at 1.5 and 24 hr post dose.
Urinalysis: Day 15.
At sacrifice on day 29, the following were examined:
The number of copora lutea.
The number and distribution of embryofetal/fetal deaths.
The individual fetal weight was determined.
The fetal abnormalities were determined.
Pre- or post-implantation loss as a percentage was determined.

Embryofetal deaths were classified as early (placenta visible at determination) and late (placental and embryonic remnants visible at examination. Abortion was evident by implantation site scars at necropsy.

Fetus

They were examined externally, sexed and weighed.
Half were examined for visceral abnormalities and the other half were examined for skeletal abnormalities. Structural changes were classified as malformation, anomalies or variants.

Litter weight and mean fetal weight were calculated from individual fetal weight. Values were expressed based on within individual litters, and group values were derived as a mean of the individual litter values.

Structural changes were identified as:

Malformations: Rare and/or probably lethal, e.g. Amelia, exencephaly.

Anomalies: Minor differences from normal that are detected relatively frequently either at initial examination, e.g. variations at the gall bladder, or at skeletal examination, e.g. hemicentric vertebra.

Variants: Alternative structures occurring regularly in the control population. They may be permanent structures, e.g., an extra pair of ribs, or they may be transient stages of development, e.g. unossified sternabra(e).

Results

Mortality: The number of deaths, killed for humane reasons, non-pregnant, abortion and those with live fetuses on day 29 is listed in the table excerpted from the report. One control animal was found on day 25. The cause was not established, but there was reduced or no fecal output, cold ears, dark eyes, unsteady gait and blood on the tray. Two HD levocetirizine rabbits were killed 1-2 days after dosing showed marked weight loss (2) slow respiration (1) and the other showed dark eyes and blood on the tray paper. The third animal killed on day 25 showed labored breathing, dark eyes, unsteady gait and lethargy. Autopsy indicated that the cause of death was consistent with decreased food intake. The cetirizine-treated animal was found dead on day 25. Autopsy indicated that death was due to an intubation error.

Category	No. of animals at dosage (mg/kg/day)				
	ucb 28556				cetirizine
	Control	30	60	120	120
Mated	16	16	16	16	16
Dead	1	0	0	0	1
Killed	0	0	0	3	0
Non-pregnant	2	0	0	0	1
Abortion	0	1	0	0	1
With live young at Day 29	13	15	16	13	13

Clinical signs: Levocetirizine, none in the surviving animals; cetirizine, one animal aborted; it showed reduced food input and/or reduced fecal output. Other signs were dilated pupils and hyperpnea.

Body weight gained: Levocetirizine, no change; cetirizine, transient decrease on days 8 and 10.

Food consumption: Levocetirizine, Days, 6-18, LD, +19%; MD, +25%; HD, +16%; cetirizine, no change.

Corpora lutea: Levocetirizine, MD, +21%; HD, 19% cetirizine, no change.

Implants, pre- and post implantation loss, embryonic deaths, no. of live young, litter weight sex ratios and mean fetal weight: No change for levocetirizine and cetirizine.

Malformations and visceral and skeletal anomalies based on incidence in litters: None for both levocetirizine and cetirizine.

Skeletal variants: levocetirizine, none; 13 ribs, C, 52% cetirizine, 77%. In another study cetirizine at 135 mg/kg, orally produced a high incidence of skeletal minor anomalies (See NDA 19-835).

Toxicokinetics: The plasma levels on days 1 and 13 are shown in the following table excerpted from the submission.

Results are expressed in µg/ml

		ucb 28556			ucb P071	
	Daily dose	30 mg/kg	60 mg/kg	120 mg/kg	120 mg/kg	
					ucb 28556	ucb 28557
Day 1	Peak	19.8 ± 10.2	33.8 ± 4.2	75.6 ± 18.1	47.1 ± 8.1	39.5 ± 7.2
	Trough	0.10 ± 0.06	0.28 ± 0.25	1.23 ± 1.50	0.90 ± 0.21	0.77 ± 0.19
	Peak/Trough ratio	202 ± 52	180 ± 109	136 ± 117	55 ± 17	55 ± 17
Day 13	Peak	23.6 ± 15.2	38.7 ± 6.3	95.7 ± 17.0	51.3 ± 8.2	42.9 ± 6.2
	Trough	0.18 ± 0.22	0.20 ± 0.10	1.11 ± 1.38	0.49 ± 0.23	0.42 ± 0.19
	Peak/Trough ratio	227 ± 147	226 ± 93	196 ± 144	125 ± 62	118 ± 52

Study Outcome

Levocetirizine and cetirizine at a comparable high dose were not teratogenic in rabbits. Cetirizine produced a slight increase in the incidence of skeletal variants.

2.6.6.7 Local tolerance: No studies were submitted.

2.6.6.8 Special toxicology studies

Cytotoxicity of levocetirizine, S-cetirizine and cetirizine on primary cultures of rat hepatocytes, No. RRLE95L0502.

In an non-GLP study, the cytotoxicity of levocetirizine, S-cetirizine and cetirizine was determined in rat hepatocytes following incubation for 3+ 21 hr recovery and incubation for 24 hrs. The results using the most sensitive biomarker, ^{3}H leucine, in the following table show the all 3 compounds were equally cytotoxic which did not increase with exposure.

Compound	Duration of Exposure, hr.	IC_{50}, mmol/L
Levocetirizine	3	0.63
S-cetirizine	3	0.67
Cetirizine	3	0.74
Levocetirizine	24	0.59
S-cetirizine	24	0.50
Cetirizine	24	0.50

2.6.6.9 Discussion and Conclusions

Acute toxicities were conducted with levocetirizine in mice, rats and dogs. At lethal doses, the toxic symptoms were similar, quiet behavior, jerky breathing, ptosis, arched back ventral lying position and piloerection. By the intravenous administration, death from a high dose was rapid. An intravenous study was conducted comparing the toxicity of levocetirizine, cetirizine and S-cetirizine. The lethal doses were similar with levocetirizine and cetirizine and were slightly higher than S-cetirizine. The only sign observed other than emesis was diarrhea following oral administration.

Multidose oral toxicity studies of 4- and 13-weeks were conducted in rats and dogs. In a 4-week toxicity rat study, the toxicity of levocetirizine and S-cetirizine were compared at 25, 75 and 225 mg/kg. Toxicity was prevalent in males with both compounds involving the targeted organ, the liver. There was increased liver weight, hepatic centrilobular and midzonal enlargement resulting in enzyme induction (increased metabolic liver enzymes), hepatic vacuolation and midzonal fat. Enzyme induction is not toxicologically relevant. Similar liver findings were seen in males in the 13-week oral studies where levocetirizine was tested at 4, 8, 25 and 75 mg/kg in one study and in a second study at 18.7, 37.5 and 75 mg/kg with 37.5 and 75 mg/kg of cetirizine. In the latter study, similar liver findings were seen with cetirizine indicating the in rats, there was no difference in the toxicity profile of levocetirizine and cetirizine.

In dogs, 4- and 13- week oral toxicity studies were conducted. In a 4-week study, levocetirizine and S-cetirizine were tested at 15, 45 and 135 mg/kg. Levocetirizine was more toxic than S-cetirizine since at 135 mg/kg, animals were in a moribund state that 3 animals were killed, and the dose of levocetirizine was lowered to 90 mg/kg. On of the finding in the necropsied animals was fecal impaction. The targeted organ was the gastrointestinal tract. At this dose S-cetirizine treated animals showed no severe toxicity. Both compounds produced similar incidences of emesis at the MD and HD. No other toxicity was observed. In a second 4-week oral toxicity study, cetirizine was tested along with levocetirizine and S-cetirizine. The oral doses were 33.75, 67.5 and 135 mg/kg for

levocetirizine and S-cetirizine and 135 mg/kg for cetirizine. Both the HD of levocetirizine and the dose of cetirizine were toxic putting the animals in a moribund state necessitating that these animals be killed and the dose lowered to 90 mg/kg. The toxicity seen with these animals were similar, i.e., emesis, tremors and fecal impaction. Two HD S-cetirizine dogs died towards the end of the study. The toxicity profile was similar to levocetirizine, but not severe enough to lower the dose during the study. All three compounds produced emesis at all doses. At termination, fecal impaction was seen at the MD and HD levocetirizine-treated animals and in the cetirizine- treated animals. The targeted organ for the three compounds was the gastrointestinal tract. There were no differences in the toxicity profile of levocetirizine and cetirizine

In a 13-week oral toxicity study, levocetirizine was tested at 8, 25 and 75 mg/kg. Emesis occurred at all doses in the females and in the HD males. No other toxicity was noted. The targeted organ was the gastrointestinal tract.

In a second 13-week oral toxicity study, 37.5 and 75 mg/kg of levocetirizine and 75 mg/kg of cetirizine were tested. Emesis was seen with both doses of levocetirizine and the dose of cetirizine. No other treatment related toxicity was observed. The targeted organ was the gastrointestinal tract.

Levocetirizine was not mutagenic in the Reverse Bacterial Mutation Assay and not genotoxic in the Mouse Lymphoma, Chromosomal Aberration and Micronucleus Assays

In a fertility and early development study, cetirizine at 5, 30 and 2000 mg/kg, orally did not affect fertility in both sexes and early fetal development. In an embryofetal development study in rats, levocetirizine at 50, 100 and 200 mg/kg, orally and cetirizine at 200 mg/kg, orally were not teratogenic. In an embryofetal development study in rabbits, levocetirizine at 30, 60 and 120 mg/kg, orally and cetirizine at 120 mg/kg, orally were not teratogenic.

There was no difference in toxicity between levocetirizine and cetirizine in the 4-and 13-week toxicity studies in rats and dogs and in the embryofetal developmental study in rats and rabbits.

2.6.6.10 Tables and Figures: None.

2.6.7 TOXICOLOGY TABULATED SUMMARY: NA.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Levocetirizine is the R-enantiomer of the marketed cetirizine. The long term oral toxicity, fertility and early developmental and prenatal postnatal developmental toxicity studies with cetirizine represent the toxicity profile of levocetirizine with supplemental bridging toxicity, developmental and genotoxicity studies conducted with levocetirizine.

Cetirizine

In acute intravenous toxicity study in the mouse, toxicity and lethality were seen at 320 mg/kg. The toxic signs were unsteady gait, dyspnea, decreased motor activity, jerks, side lying paddling movements, tremors; deaths occurred within 6 days and at 420 mg/kg, all mice died within 10 min following administration.

In chronic toxicity studies in mice and rats with cetirizine, the liver was the target organ, in males. The liver changes were the result of enzyme induction and were reversible. Livers also showed fat deposition. In Beagle dogs, the targeted organ was the gastrointestinal tract. The clinical signs depending on the dose were emesis, salivation, tremors, quiet behavior, ataxia and hypothermia, loose mucus feces. In the carcinogenicity studies in rodents, the dietary doses were 1, 4 and 16 mg/kg for the mouse and 3, 8 and 20 mg/kg for the rat. The rats showed liver toxicity (hypertrophy, vacuolation and fat deposit). No tumors were seen in rats that were clinically significant, while male mice showed benign liver tumors which were due to enzyme induction.
In genotoxicity studies, cetirizine was negative in the Ames, Human Peripheral Lymphocytes Chromosomal Aberration, Mouse Lymphoma and Mouse Micronucleus assays.
In reproductive toxicity studies with cetirizine, mice were used in the Fertility and Early Development (4, 16, 64 mg/kg), Embryofetal Developmental (6, 24, 96 mg/kg) and Prenatal and Postnatal Development studies (6, 24, 96 mg/kg). There was no effect on fertility, but increased skeletal anomalies/variants (MD, HD) in the fertility and early developmental study and no effect in the embryofetal developmental study. In the prenatal and postnatal development study, there was at the HD decreased pup weight. In rabbits, cetirizine at 75 mg/kg orally, did not affect embryofetal development.
In rats, cetirizine at oral doses of 5, 30 and 200 mg/kg were tested in both sexes in the fertility and early developmental studies. Cetirizine did not affect sperm dynamics, fertility and early fetal developmental.

Levocetirizine

Studies show that levocetirizine was a competitive inhibitor of the H_1 receptor. In in vitro binding studies, levocetirizine was more potent (1-4 x) than cetirizine. Levocetirizine was 2 times as potent as cetirizine in inhibiting the binding to the human H_1 receptors (Ki: 3nM vs. 6 nM). In the in vitro tracheal and isolated guinea pig ileum preparations, levocetirizine antagonized histamine-induced contractions. In these studies levocetirizine was 2-4 x more potent than cetirizine. In an in vivo preparations, levocetirizine intravenously inhibited histamine induced bronchospasms in anesthetized guinea pigs that was twice that of cetirizine. In inhibiting the histamine induced wheal test in mice and rats, levocetirizine was 2-4 times more potent than cetirizine and in dogs, the activity of levocetirizine 0.15 mg/kg was more active than cetirizine (58% vs.48%). In all studies levocetirizine and cetirizine were more potent than S-cetirizine. The in vitro antihistaminic activity of levocetirizine was 9 times more potent that P026, a metabolite of cetirizine.
The activity of levocetirizine was weak in inhibiting the binding of 12 other radioligands.
Safety Pharmacology studies were conducted with levocetirizine in mice, rats and dogs. A single oral (46, 138, 462 and 1384 mg/kg) and intraperitoneal (14, 46, 92 and 138 mg/kg) dose study was conducted in mice, By the oral route, tremors piloerection, decreased motor activity and muscle tone were seen initially at 138 mg/kg and progressed until death at 462 mg/kg. By the intraperitoneal route, these changes began at 46 mg/kg and progressed until death at 138 mg/kg. In rats, doses of 25, 50 and 100 mg/kg, orally levocetirizine produced no central nervous system depression as determined by the Irwin

test. In mice, levocetirizine potentiated hexobarbital sleeping time and in rats did not affect pentobarbital sleeping time. Levocetirizine did not show significant central nervous system effects.

In evaluating the effect on the cardiovascular system, in vitro and in vivo studies were conducted. In the Xenopus laveis oocytes hERG K+ assay, both levocetirizine and cetirizine were inactive at 30 uM, but in the guinea pig K+ current effects using ventricular myocytes assay blockage by both levocetirizine and cetirizine were equally effective at 0.1 mM showing comparable activity. Levocetirizine at 30 and 300 uM (both are high concentrations) inhibited the potassium channel by prolonging the action potential duration of the dog isolated Purkinje fibers and did not affect the maximal diastolic potential (MDP), action amplitude amplitude (APA) and the maximum upstroke velocity of phase 0 of the action potential (Vmax). Since levocetirizine did not affect the maximum upstroke velocity indicates that the sodium channel was not affected. In anesthetized rats, levocetirizine at intravenous doses of up to 25.9 mg/kg produced a transient decrease in diastolic pressure and heart rate. In anesthetized dogs, cumulative intravenous doses starting at 4.6 mg/kg and ending at 138.2 mg/kg produced bradycardia at 4.6 mg/kg; at doses $\geq$ 46.2 mg/kg, there were transient tachycardia, disturbance of conduction and repolarization and death. In another study, levocetirizine at cumulative intravenous doses up to 10 mg/kg in anesthetized dogs did not affect the cardiovascular and respiratory systems. In a gastrointestinal study in rats, levocetirizine at oral doses up to 100 mg/kg did not affect gastrointestinal transit time.

In distribution studies in rats, the highest concentrations were seen in the liver, kidney, pancreas and gastrointestinal tract. Radioactivity in the placenta, fetus and brain were less than background. In dogs, the highest concentration was in the bile, liver and kidneys. The brain shows levels that were 12% of plasma level and 19% of the blood level. However, the average ratio of tissue radioactivity in the brain to plasma unbound levocetirizine levels was 2.8 at 24 hours post dose. In rats, the main metabolites were M1, M2, F11 and F12. In dogs, the major metabolites were M7+M8 (16-23% of the dose) and M10 (8-13% of the dose) along with unchanged levocetirizine.

In acute toxicity studies, there was no difference in the toxicities between levocetirizine and cetirizine.

Multidose oral toxicity studies of 4-and 13- weeks were conducted in rats and dogs.

In a 4-week study in rats, the toxicity of levocetirizine and S-cetirizine at the same doses showed a similar toxicity profile with hepatic centrilobular and midzonal enlargement, increase liver enzymes, hepatic centrilobular and midzonal fat and hepatic vacuolation. The liver enzyme increases were due to enzyme induction. The target organ was the liver. All the changes were reversible.

In a 13-week oral toxicity study in rats, only salivation was the clinical sign. Males showed an increase in central lobular vacuolation central fat deposition and increased liver enzymes. The target organ was the liver. All the changes were reversible.

In a second 13-week oral toxicity study in rats with levocetirizine, cetirizine was included. Both compounds induced enzymes and hepatic fat deposition. The target organ was the liver; both compounds showed a similar toxicity profile.

Two 4-week and two 13-week oral toxicity studies were conducted in dogs. In the first 4-week study both levocetirizine and S-cetirizine; levocetirizine was toxic and lethal at the HD requiring the dose to be lowered to 90 mg/kg on day 8.The HD of S-cetirizine

showed only emesis and hypersalivation; in addition, the levocetirizine treated animals showed tremors and instability. Significant increase in the incidence of emesis occurred at the MD and HD for both compounds, a toxicity common for both enantiomers. At the HD, both compounds produced increased urine volume. The target organ was the gastrointestinal tract for both compounds.

In the second 4-week oral study in dogs, the test compounds were levocetirizine, S-cetirizine and cetirizine. Two female HD levocetirizine treated animals were killed in a moribund condition which was treatment related. For S- cetirizine 2 HD females were killed in a moribund condition and 1 MD female died due to bronchopneumonia resulting from aspiration of the vomitus. The HD of levocetirizine and cetirizine were reduced to 90 mg/kg from days 11/18. Emesis was seen at all doses of the 3 compounds. There was a 15% increase in the Qtc interval in the levocetirizine treated animals which was not confirmed. Fecal impaction was seen at the MD and HD levocetirizine and in the cetirizine treated animals and not in the S-cetirizine treated animals. Histopathology seen in the trachea of levocetirizine and S-cetirizine treated animals was not confirmed in another 4-week oral study at the same dose. The target organ was the gastrointestinal tract, and all the changes were reversible.

In a 13-week oral toxicity study in dogs, levocetirizine caused increased incidence of emesis occurred in the HD males and in all the doses in females showing increased sensitivity. The targeted organ of toxicity was the gastrointestinal tract and the findings were reversible.

In the second oral 13-week toxicity study in dogs, the toxicity of levocetirizine and cetirizine was compared. Both induced emesis at the doses tested. At week 13, there was at 75 mg/kg of levocetirizine and cetirizine a 7% increase in Qtc in females. This low increase is not of clinical concern. Further, the increased Qtc with levocetirizine was not confirmed at the same dose in the other 13-week study. The changes in hematological, clinical chemistry, liver and salivary weight changes and histological changes in the testes and liver were not treatment related since they were not confirmed in another 13-week study. The gastrointestinal tract was the target organ of toxicity. Both compounds showed a similar toxicity profile.

Levocetirizine was not mutagenic in the Reverse Bacterial Mutation assay and not genotoxic in Mouse Lymphoma assay and in one Micronucleus assay. Six Human Lymphocyte Aberration assays were conducted. The conclusion was that levocetirizine was not genotoxic. This was based on a positive response that was not confirmed or the positive response occurred at an excessive cytotoxic concentration and lower concentrations were negative.

In fertility and early developmental studies in rats, cetirizine at oral doses up to 200 mg/kg were tested in both sexes. Cetirizine did not affect sperm dynamics, female fertility and early fetal developmental.

Embryofetal developmental studies were conducted in rats and rabbits. In pregnant rats, oral doses of 50, 100 and 200 mg/kg of levocetirizine and 200 mg/kg of cetirizine were tested. Levocetirizine and cetirizine did not produce skeletal and visceral malformations, anomalies or skeletal variants. In an embryofetal development study in rabbits, levocetirizine at 30, 60 and 120 mg/kg, orally and cetirizine at 120 mg/kg, orally were not teratogenic. However, cetirizine produced a slight increase in the incidence of skeletal variants.

Conclusion

The toxicity profile of levocetirizine and cetirizine was similar.

Unresolved toxicology issues (if any): None.

Recommendation:

Approval of NDA 22-064 with the recommended label changes.

Labeling

The following are recommendations in **BOLD** and ~~Strikout~~ with justification in the labeling. See attachments for the animal to human dose ratios incorporated in the label.

Pregnancy Category B

(b) (4)

Response

In the rat teratogenic study, the oral dose was 200 mg/kg and not 260 mg/kg.
The ratios on a mg/m^2 basis were based on a 50 kg adult.

Overdosage

(b) (4)

Response

The label should also contain the animal to human ratio for a 6 year old child.
The ratios are based on a 50 kg adult and on a 20 kg for a 6 year old child.

Mechanism of Action

(b) (4)

Response

The statement regarding the dissociation time of 115 min vs. 95 min was not statistically significant (115 ± 38 min vs. 95± 33 min); therefore, there was no difference between the duration of the dissociations.

(b) (4)

Response

No anticholinergic and serotoninergic activity was submitted for levocetirizine.

(b) (4)

Response

Only the results of 12 in vitro non-H_1 receptors binding studies were submitted.
This does not imply that levocetirizine does not bind to all non-H_1 receptors as indicated in the proposed statement.

(b) (4)

Response

The autoradiographic studies in rats indicated that levocetirizine was present in the brain at levels below the background. In the dog, the tissue and organ radioactivity/plasma unbound levocetirizine level ratios at 48 hrs following repeated daily oral administration for 8 days of 1 mg/kg was 4.61 for the brain stem, 4.03 for the cerebellum and 4.49 for the cerebrum.

(b) (4)

Response

Only in vitro data were submitted for levocetirizine. It showed that levocetirizine occupied H_1 mouse cerebral cortex receptors.

Distribution

(b) (4)

Response

Animal information should not be in the distribution section since this section involves only human pharmacokinetics.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

(b) (4)

(b) (4)

Response

The proposed statements did not reveal the (b) (4) in (b) (4) and (b) (4) should replace (b) (4) in the text.

(b) (4)

Response

Mice and not rats were used in the Micronucleus test.

(b) (4)

Response

Data from toxicity studies regarding spermatogenesis are not appropriate to be described in the fertility section.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Drug: **Levocetirizine NDA 22-064**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric		2.5	1	2.5	20	0.125	25	3.125
Adult	>12	5	1	5	50	0.1	37	3.7

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	oral		6	0	---	---		
rat	oral		6	0	---	---		
mouse	oral		3	0	---	---		
dog			20	0	---	---		
mouse	oral		3	0	---	---		
Repro/Fertility:								
rat	oral		6	0	---	N/A		
rat	oral		6	0	---	N/A		
mouse	oral		3	0	---	N/A		
mouse	oral		3	0	---	N/A		
Teratogenicity:								
rabbit	oral	120	12	1440	389.19	N/A	390	
rat	oral	200	6	1200	324.32	N/A	320	
rat			6	0	---	N/A		
rabbit			12	0	---	N/A		
extra			---	---	---	N/A		
Overdosage:								
mouse	oral	240	3	720	194.59	230.4	200	230
rat	oral	240	6	1440	389.19	460.8	390	460
rat	oral		6	0	---	---		
rat			6	0	---	---		

Drug: **Cetirizine**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	6	5	1	10	20	0.5	25	6.25
Adult	>12	10	1	10	50	0.2	37	7.4

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	oral	20	6	120	16.216	19.2	16	20
rat	oral		6	0	---	---		
mouse	oral	16	3	48	6.4865	7.68	7	8
dog			20	0	---	---		
mouse	oral	4	3	12	1.6216	1.92	2	2
Repro/Fertility:								
rat	oral		6	0	---	N/A		
Rat	oral		6	0	---	N/A		
Mouse	oral	96	3	288	38.919	N/A	40	
Mouse	oral	64	3	192	25.946	N/A	25	
Teratogenicity:								
Rabbit	oral		12	0	---	N/A		
Rat	oral		6	0	---	N/A		
Rat			6	0	---	N/A		
Rabbit			12	0	---	N/A		
Extra			---	---	---	N/A		

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/s/

Lawrence Sancilio
8/21/2007 10:54:06 AM
PHARMACOLOGIST

Joseph Sun
8/21/2007 04:05:18 PM
PHARMACOLOGIST
I concur.

NDA Pharmacology Fileability Check List

NDA No: 22-157

Date of submission: 3/27/07

Date of Fileability meeting: 5/11/07

Information to Sponsor: Yes (X) No ( )

Note: In the letter of submission, the sponsor indicated that the nonclinical data were cross referenced to NDA 22-064. However, in the CTD, under Module 2, 2.6 Nonclinical written and tabulated summaries and under Module 4, Nonclinical Pharmacology and Toxicology, is written, Not Required for This Submission. In these sections, the preclinical information or the appropriate statement, e.g. reference to NDA 22064 should be made. It is assumed that the requested information will be submitted.

Date of check list: 5/9/07

(1) On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review? Yes (X) No ( ) NA ( ).

(2) On its face, is the Pharm/Tox section of the NDA legible for review?
Yes (X) No ( ) NA ( ).

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Yes (X) No ( ) NA ( ).

	Yes	No	NA
Pharmacology	( )	( )	(X)
ADME	( )	( )	(X)
Toxicology (duration, route of administration and species specified)			
acute	( )	( )	(X)
subchronic and chronic studies	( )	( )	(X)
reproductive studies	( )	( )	(X)
carcinogenicity studies	( )	( )	(X)
mutagenicity studies	( )	( )	(X)
special studies	( )	( )	(X)
others	( )	( )	(X)

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes ( ) No (X) NA ( ).

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes ( ) No ( ) NA ( ).

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57? Yes (X) No ( ).

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes ( ) No ( ) NA (X).

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes (X) No ( ) NA ( ).

If not, has the applicant submitted a rationale to justify the alternative route?
Yes ( ) No ( ) NA ( ).

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes (X) No ( ) NA ( ).

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes ( ) No (X) NA ( ).

However, there are impurities/degradant issues which may require qualification.

(10) Are there any outstanding preclinical issues? Yes ( ) No (X).

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ( ) NA ( ).

If no, state below why it is not.

(12) Should any additional information/data be requested? Yes (X) No ( ). See below the letter to the sponsor.

NDA Planning Timeline

NDA No.: 22-157

Date of planning timeline:	8/9/07
PDUFA Due Date:	1/28/08
Projected review completion date:	8/15/07

	Milestone Dates
Pharmacology and ADME	NA
Toxicology	NA
General toxicity studies	NA
Carcinogenicity studies and mutagenicity studies	NA
Reproductive studies	NA
Special studies and others	NA
Labeling	8/15/07

Letter to the Sponsor:

In your letter of March 27, 2007 submitting NDA 22-157, nonclinical data were not submitted but cross referenced to NDA 22064. However, in the CTD map, under Module 2, 2.6 Nonclinical Written and Tabulated Summaries and under Module 4, Nonclinical Pharmacology and Toxicology, was written, Not Required for This Submission. This statement is not acceptable for these sections of the CTD. Provide in these sections the appropriate statement or information, e.g., reference to NDA 22-064.

Signatures (optional):

Reviewer Signature _____
Lawrence F. Sancilio, Ph.D.

Supervisor Signature _____
C. Joseph Sun, Ph.D.

Concurrence Yes ___ No ___

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

/s/

Lawrence Sancilio
5/9/2007 04:37:35 PM
PHARMACOLOGIST

Joseph Sun
5/14/2007 09:58:50 AM
PHARMACOLOGIST
I concur.