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*APPLICATION NUMBER:*

**22-064**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA:</b>	22-064
<b>Type:</b>	505(b)(2)
<b>Generic Name:</b>	Levocetirizine dihydrochloride
<b>Indication:</b>	Seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children $\geq 6$ yrs.
<b>Dosage Form:</b>	Tablet
<b>Strength:</b>	5 mg (scored)
<b>Route of Administration:</b>	Oral
<b>Dosing regimen:</b>	Once daily
<b>Applicant:</b>	UCB Inc.
<b>OCP Division:</b>	DCP2
<b>Clinical Division:</b>	DPADP (OND-570)
<b>Submission Date:</b>	July 25, 2006
<b>Reviewer:</b>	Partha Roy, Ph.D.
<b>Team Leader:</b>	Emmanuel Fadiran, Ph. D.
<b>Pharmacometric Reviewer:</b>	Christine Garnett, Ph.D.
<b>Pharmacometric Team Leader:</b>	Joga V. Gobburu, Ph.D.

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## 1 EXECUTIVE SUMMARY

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-064's Clinical Pharmacology information submitted on July 25, 2006 and finds it acceptable provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the package insert.

### 1.2 PHASE IV COMMITMENTS

None

### 1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Levocetirizine dihydrochloride, the active component of Xyzal (proposed trade name), is an orally active H<sub>1</sub>-receptor antagonist. The sponsor submitted NDA 21-064, to seek approval for the daily oral administration of an immediate-release 5 mg levocetirizine scored tablet intended for the treatment of symptoms associated with allergic rhinitis conditions, such as seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU). Levocetirizine is the R-enantiomer of the racemate cetirizine. This is a 505(b)(2) application where the sponsor is relying on the Agency's previous findings of safety and efficacy of cetirizine, the second generation antihistamine approved as Zyrtec®.

Levocetirizine is a highly soluble  and a moderately permeable (approximately  of radioactivity excreted in urine in a mass balance study) drug that exhibits dose-dependent increase in systemic exposure over the  dose range, across multiple studies. The permeability of levocetirizine  was determined to be intermediate. It is a rapidly dissolving (> 85% within 15 minutes) drug product.

Twenty-five (25) clinical pharmacology studies were submitted to support human PK and biopharmaceutics of the product, out of which 8 studies, including 1 pivotal bioequivalence study and 1 pharmacodynamic (wheal and flare) study were reviewed in detail.

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after dosing. Steady state is achieved after two days with minimal accumulation (~12%), consistent with the half-life estimate of 7-8 hrs obtained from single-dose data. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. In cross-study comparisons, the plasma levocetirizine concentration in healthy subjects increases approximately proportionally with increasing levocetirizine

doses of 2.5 to 30 mg. Food had no effect on the extent of exposure (AUC) of the levocetirizine tablet, but  $T_{max}$  was delayed by about 1.25 hours and  $C_{max}$  was decreased by about 36% after administration of the drug with a high fat meal; therefore, levocetirizine can be administered without regard to food.

Levocetirizine is about 90% bound to plasma proteins in healthy subjects following administration of 5 mg levocetirizine. The average apparent volume of distribution of levocetirizine is approximately 27 L in healthy subjects, representative of distribution in total body water.

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore, differences resulting from genetic polymorphism or concomitant intake of drug metabolizing enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation, and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involves multiple and/or unidentified CYP isoforms. Levocetirizine, at concentrations well above  $C_{max}$  level attained after administration of therapeutic doses, is not an inhibitor of CYP enzymes 1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and is also not an inducer of CYP enzymes 1A2, 2C9 and 3A4 and UGT1A1. These data, taken together, indicate that levocetirizine is unlikely to produce, or be subject to metabolic interactions.

After administration of single-dose 10 mg levocetirizine, none of the plasma samples exhibited detectable or measurable levels of dextrocetirizine (study A221). However, in the same study, several urine samples from 20 out of 24 subjects detected dextrocetirizine. In another phase 2 study (A00265), plasma samples obtained from several subjects after the last dose following 4-weeks of once-daily levocetirizine treatment exhibited measurable levels of dextrocetirizine. Two possible sources of dextrocetirizine following levocetirizine dosing are: 1) conversion of levocetirizine (R-form) to dextrocetirizine (S-form) and/or 2) conversion of levocetirizine (R-form) to dextrocetirizine (S-form). Therefore, chiral inversion of R-cetirizine (levocetirizine) to the dextrocetirizine (S-form) cannot be completely ruled out even though the extent of such conversion is not significant.

The mean apparent total body clearance for levocetirizine was approximately 0.63 mL/min/kg. The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Renal clearance of levocetirizine correlates with that of creatinine clearance. In patient population with PAR following repeated administration of 2.5 mg to 10 mg, dose dependent increase in plasma levels was achieved while total body clearance, half-life, and relative urinary excretion are all independent of dose.

No thorough PK/PD study has been performed with levocetirizine, however, two studies included both PK and PD assessments: histamine-induced wheal and flare in one study, and IgE-dependent hypersensitivity cutaneous reaction following experimental antigenic stimulation in the other study. The levocetirizine plasma concentrations peaked during the first 2 hours post-dose followed by a rapid decline. The peak pharmacodynamic

effects on the other hand are generally observed within 3 to 6 hours and maintained for at least 24 hours post-dose. There was no PK/PD modeling performed, however the above data suggests that there may not be any direct PK/PD relationship for levocetirizine.

A thorough QT study was conducted following the current ICH E-14 Guidance. In this single dose, crossover study in healthy male and female subjects, levocetirizine did not appear to prolong the QTc interval in a clinically meaningful way. After baseline and placebo adjustment, the maximum mean QTc change was 3 msec (1-sided 95% upper confidence interval: 7 msec) for the 5 mg dose and -1 msec (1-sided 95% confidence interval: 2 msec) for the 30 mg dose at 4 hours and 24 hours, respectively, following drug administration. Used as a positive control, moxifloxacin (400 mg) had a maximum mean QTc change of 14 msec (1-sided 95% Upper confidence interval: 17 msec) after baseline and placebo adjustment at 4 hours following drug administration. Further details can be found in the QT study (A00419) review by the IRT team dated March 7, 2007.

No levocetirizine pharmacokinetic studies in adolescents (12 to 17 years) and children (6 to 11 years) were submitted as part of this application. However, literature data (Simons FER and Simons KJ 2005) reported about 2-fold increase in systemic exposure of levocetirizine in children 6 to 11 years compared to adult participants in the pivotal bioequivalence study (Table 1). Consistent with the exposure data, the total body oral clearance in children was found to be about 43% lower compared to adults following oral dosing. The mean time to peak plasma concentration is slightly prolonged in children compared to adults (1.2 vs. 0.86 hr).

**Table 1.** Mean (SD) pharmacokinetic parameters in adults ages  $\geq 18$  years (study A232) and in children ages 6-11 years.

Dose = 5 mg	AUC (ng.hr/mL)	C <sub>max</sub> (ng/mL)	C <sub>24h</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	CL/f (mL/min/kg)	V <sub>d</sub> /f (L/kg)
Adults (18-55 yrs)	1614 (542)	216 (47)	20 ± 10	0.86 (0.42)	7.5 (1.4)	0.63 (0.14) [44]*	0.41 (0.08) [25 L]
Children (6-11 yrs)	3549 (342)	450 (37)	26 ± 13	1.2 (0.72)	5.7 (0.2)	0.82 (0.05) [25]*	0.40 (0.02) [12 L]
Adolescent (12-17 yrs)			74 ± 24*				

\* expressed as mL/min assuming 30 kg for an average child and 60 kg for an average adult

\*\*C<sub>17h</sub> after 4 weeks of treatment

Reference: Simons FER and Simons KJ: J Allergy Clin Immunol 2005; 116:355-61.

Among the intrinsic and extrinsic factors studied (age, gender, BMI, high fat food), only gender (intrinsic) and food (extrinsic) appear to have modest effects on the pharmacokinetic parameters of levocetirizine. The half-life tends to be slightly shorter in women (7.1 ± 1.7 h) than in men (8.6 ± 1.8 h). However, the difference disappeared when the data was adjusted for body weight such that adjusted clearance in women (0.7 ± 0.2 mL/min/kg) was comparable to that in men (0.6 ± 0.1 mL/min/kg). The effect of food is observed mainly for T<sub>max</sub> and C<sub>max</sub>, but not for AUC. Age exhibited a tendency to increase half-life and to decrease oral total body clearance, but, as the PK studies did not include subjects older than 65 years, the effect of age could not be fully characterized.

Systemic exposure, as evidenced by AUC, exhibited 1.8-, 3.2-, 4.3-, and 5.7-fold increase in mild, moderate, severe renal impaired and end-stage renal disease (ESRD) patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, 2.9-, and 4-fold, respectively. The apparent clearance of levocetirizine was shown to be correlated with the creatinine clearance and was progressively reduced with the severity of renal impairment. Protein binding was independent of the degree of renal impairment. Based on the exposure data, this reviewer explored different dosing scenarios for renal impaired patients and came up with the following dosing recommendation that is different from what the sponsor proposed:

Sponsor's dosing proposal: \_\_\_\_\_ QD for healthy and mild renal impaired; \_\_\_\_\_ for moderate renal impaired; \_\_\_\_\_ severe renal impaired; contraindicated in patients with  $CL_{CR} < 10$  mL/min and ESRD patients.

Reviewer's dosing recommendation: 5 mg QD for healthy; 2.5 mg QD for mild renal impaired; 2.5 mg once every 2 days for moderate renal impaired; 2.5 mg twice weekly, i.e. once every 3 or 4 days for severe renal impaired; contraindicated in patients with  $CL_{CR} < 10$  mL/min and ESRD patients.

The sponsor did not conduct any pharmacokinetic study in hepatic impaired subjects. From study A230 (Renal Impairment Study), the non-renal clearance was found to constitute about 28% of the total clearance in healthy adult subjects. Since, majority of the drug is cleared via urine, hepatic clearance constitutes a relatively minor pathway of drug elimination. However, in the absence of a specific study, the effect of hepatic impairment on levocetirizine PK remains undetermined.

The formulation proposed for registration is the same tablet (except for scoring) as that used in all clinical trials with the exception of one of the pivotal trials where a heavier tablet was used to allow for blinding with the active comparator. The levocetirizine to-be-marketed 5 mg tablet formulation dosed was bioequivalent (in terms of rate and extent of absorption) to the heavier pivotal trial levocetirizine tablet dosed at 5 mg. *In vitro* data demonstrate that scoring has no impact on the formulation.

Reviewer  
Partha Roy, Ph.D.  
Office of Clinical Pharmacology  
Division of Clinical Pharmacology 2

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Concurrence:  
Emmanuel Fadiran, Ph.D., Team leader

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## 2 QUESTION BASED REVIEW

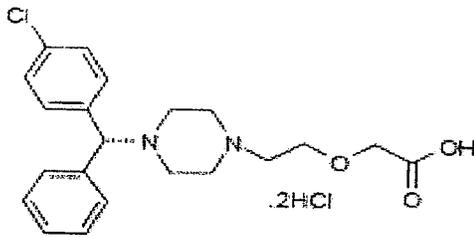
### 2.1 General Attributes

#### 2.1.1 What are the general attributes of Levocetirizine dihydrochloride?

Levocetirizine dihydrochloride has one chiral center and is the R enantiomer (ucb 28556) of the racemate cetirizine hydrochloride. Cetirizine hydrochloride is registered in the US as Zyrtec®.

Levocetirizine is believed to be the sole active enantiomer in cetirizine. The chemical name of levocetirizine dihydrochloride is (R)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy] acetic acid hydrochloride. The chemical structure of levocetirizine dihydrochloride is provided below.

#### STRUCTURAL FORMULA:



**Molecular formula:**  $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

**Molecular weight:** 461.8

**Solubility:** Levocetirizine dihydrochloride is a white to off white powder. It is freely soluble in water.

**Octanol-Water Partition Coefficient:** At pH 7.4 is  $1.32 \pm 0.03$ .

**Hygroscopicity:** Not hygroscopic

**Melting Range:** about 215 – 220 °C

#### FORMULATION

Levocetirizine dihydrochloride drug product will be supplied for oral administration as an immediate-release, white to off-white, oval film-coated scored tablet containing 5 mg of levocetirizine dihydrochloride. It is currently marketed outside the United States as a 5 mg (of the dihydrochloride salt), scored or unscored tablet, depending on the country, under a variety of trade names including Xyzal®, the trade name proposed for the United States. The scoring provides flexibility of dosing; it has no impact on the bioavailability of the drug product based on *in vitro* tests, as claimed by the sponsor.

#### INDICATION (as per proposed label)

Xyzal® (levocetirizine dihydrochloride) is indicated for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), and

for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 years of age or older.

**DOSAGE AND ADMINISTRATION (as per proposed label)**

Xyzal® is available as 5 mg scored tablet allowing for the administration of a dose of 2.5 mg if needed. The drug product can be taken with or without food.

The proposed initial dose of Xyzal® is \_\_\_\_\_

**2.2 General Clinical Pharmacology**

**2.2.1 What is known about the pharmacokinetics of Xyzal®, specifically the single- and multiple-dose PK parameters of levocetirizine after administration of Xyzal®?**

The sponsor evaluated single-dose pharmacokinetics of levocetirizine under fasted and fed conditions, the results of which are presented below in Table 2. Also presented are multiple-dose pharmacokinetics data following administration of 5 mg levocetirizine for 8 days in healthy subjects. Consistent with the half-life estimate of 7-8 hrs from single-dose study, the accumulation following repeated administration was found to be minimal (~12%). Levocetirizine was found to be rapidly absorbed with a median  $T_{max}$  of 0.75 hrs following single and repeated dosing.

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**Table 2.** Mean (SD) pharmacokinetic parameters of levocetirizine after single-dose (SD) administration under fasted and fed conditions and after multiple-dose (MD) administration of 5 mcg levocetirizine tablet for 8 days.

PK Parameters	Treatments			Ratio (Fed/Fasted)	Accumulation Ratio (MD/SD)
	Single-Dose		Multiple-Dose		
	Fed	Fasted			
C <sub>max</sub> (ng/mL)	175.0 (36.8)	269.7 (47.0)	307.7 (60.9)	0.64* (0.6, 0.7)	1.14
C <sub>24h</sub> (ng/mL)	19 (10)	20 (10)	25 (22)	–	1.25
T <sub>max</sub> <sup>a</sup> (hr)	2.0 (0.75, 6)	0.75 (0.5, 2)	0.75 (0.5, 2)	–	–
AUC <sub>0-24h</sub> (ng.hr/mL)	1639.2 (354.2)	1944.6 (389.3)	2124.2 (691.7)	0.84**	1.10
AUC <sub>0-t</sub> (ng.hr/mL)	1846.9 (485.0)	2157.5 (514.7)	–	0.85* (0.83, 0.88)	–
AUC <sub>0-inf</sub> (ng.hr/mL)	1899.8 (522.3)	2203.9 (542.4)	2476.5 (1067.5)	0.86* (0.83, 0.89)	1.12
T <sub>1/2</sub> (hr)	7.8 (1.7)	7.5 (1.4)	8.2 (2.0)	–	–
A <sub>e(0-48h)</sub> (mg)	3.72 (0.45)	3.66 (0.49)	4.53 (1.77)	1.02**	1.24

<sup>a</sup> median (range); \* ratio of geometric means (90% confidence interval); \*\* ratio of arithmetic means

### 2.2.2 How does the pharmacokinetics of levocetirizine in healthy subjects compare to that in patients with seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) or chronic idiopathic urticaria (CIU)?

The levocetirizine concentrations in patients suffering from PAR to house dust mites (studies A219, A00265) were shown to be generally comparable to the plasma concentrations found in healthy subjects following administration of 2.5 – 10 mg dose range of levocetirizine. In study A254, mean (SD) plasma concentrations at pre-dose (0 hr) and 4 hours post-dose on day 4 following once-daily administration of 5 mg levocetirizine were 27.3 (16.6) ng/mL and 198.2 (40.3) ng/mL, respectively in grass pollen allergic subjects (i.e. SAR). These concentrations were comparable to that found in healthy subjects (Table 3).

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**Table 3.** Plasma concentrations of levocetirizine as a function of the dose in healthy subjects and target patient population across multiple studies.

Population	Study No.	Daily dose (mg)	Plasma concentrations (ng/mL)	Time/interval after single/last dose (h)
Healthy volunteers	A184 (N=18)	2.5 (single)	78	4
	A232 (N=24)	5 (single)	121	4
	A221 (N=24)	10 (single)	302	4
	A238 (N=20)	5 (repeat)	2124±692 <sup>(a)</sup>	-
	A00263 (N=36)	30 (repeat)	401±165 13671±3370 <sup>(a)</sup>	12 -
Target population	A219 (N=79)	2.5	36 ± 30	13.8 ± 3.8
	(N=81)	5	79 ± 66	14.1 ± 4.0
	(N=96)	10	128 ± 83	14.1 ± 3.8
	A00265 (N=74)	2.5	41.6 ± 38.1	9.50-21.25
	(N=80)	5	79.5 ± 65.4	9.50-22.25
	(N=76)	10	162 ± 123	9.50-23

<sup>(a)</sup> AUC<sub>0-24h</sub> expressed in ng.h/mL

### 2.2.3 How does the systemic exposure of levocetirizine compare between when given as a single enantiomer (levocetirizine) and as the racemate (cetirizine)?

Through the 505(b)(2) regulatory pathway, this application relies on the comparative bioavailability data for levocetirizine following administration as a single enantiomer and as a racemate (cetirizine). The sponsor, therefore, conducted a specific comparative bioavailability study to demonstrate equivalent systemic exposure of levocetirizine following single dose oral administration when given alone (10 mg) or as cetirizine (20 mg), both given as an oral extemporaneous aqueous solution. The study demonstrated equivalent disposition of levocetirizine following single dose oral administration when given alone (10 mg) or as racemate (20 mg), both given as an oral extemporaneous aqueous solution. The 90% confidence intervals for the treatment ratios of log-transformed C<sub>max</sub>, AUC and A<sub>e</sub> were all within the 80- 125% equivalent range (C<sub>max</sub>: 95.6-105.5; AUC: 97.1-104.5; A<sub>e</sub>: 89.6-99.0).

### 2.2.3 What are the characteristics of levocetirizine distribution?

The mean apparent oral volumes of distribution (Vd/F) of levocetirizine from an extemporaneous solution (study A221) and a tablet formulation (A230) were found to be 27 L and 34 L, respectively, i.e. representing distribution in total body water. In the same study (A221), cetirizine and levocetirizine oral solutions exhibited identical estimates of apparent volume of distribution. Since bioavailability of levocetirizine was nearly complete, as evidenced by the recovery of more than 86% of the total radioactive dose in urine, the apparent volume of distribution estimate from an oral solution is very close to the true measure of levocetirizine distribution.

In a radiolabeled study (A233), radioactive components were found to be only marginally associated with blood cells, as the blood to plasma ratio was 0.51 to 0.68. The mean values of the binding to human plasma proteins are 92.6 and 89.2% for levocetirizine and cetirizine, respectively. The *ex vivo* protein binding of radiolabeled levocetirizine,

measured by ultrafiltration, is 96.1% at 1 hour (Study A233), comparable to the *in vitro* protein binding (95%) of cetirizine assessed in the same study.

Tissue concentration data are available in rats, pregnant rats and in dogs. Highest concentrations are found in liver and kidneys (tissues involved in biotransformation and excretion) and lowest concentrations in the central nervous system, lens, aqueous and vitreous humor, and adipose tissue.

#### **2.2.4 Does the mass balance study suggest renal or hepatic as the major route of levocetirizine elimination?**

The mass balance study was well conducted, reporting near complete recovery of 98% of the dose in urine and feces by 5 days, of which 96% came out by the end of 3 days. The major route of elimination was identified to be urine (86% of the dose); feces constituted a minor route (13% of the dose). Majority of the drug was found to be eliminated unchanged in urine and feces, comprising 77% and 9% of the dose, respectively over 48 hours post administration. Metabolites constitute only about 4.5% and 1% in urine and feces, respectively in the same time period. Therefore, renal excretion is determined to be the major route of levocetirizine elimination.

#### **2.2.5 What are the characteristics of levocetirizine metabolism?**

Levocetirizine is not extensively metabolized in humans. Majority of the drug was found to be eliminated unchanged in urine and feces, comprising 77% and 9% of the dose, respectively over 48 hours post administration. A total of about 90% of the radioactive dose was recovered in urine and feces by that time. The low extent of metabolism is also consistent with the long half-life measured in severe renal impaired and end-stage renal disease subjects.

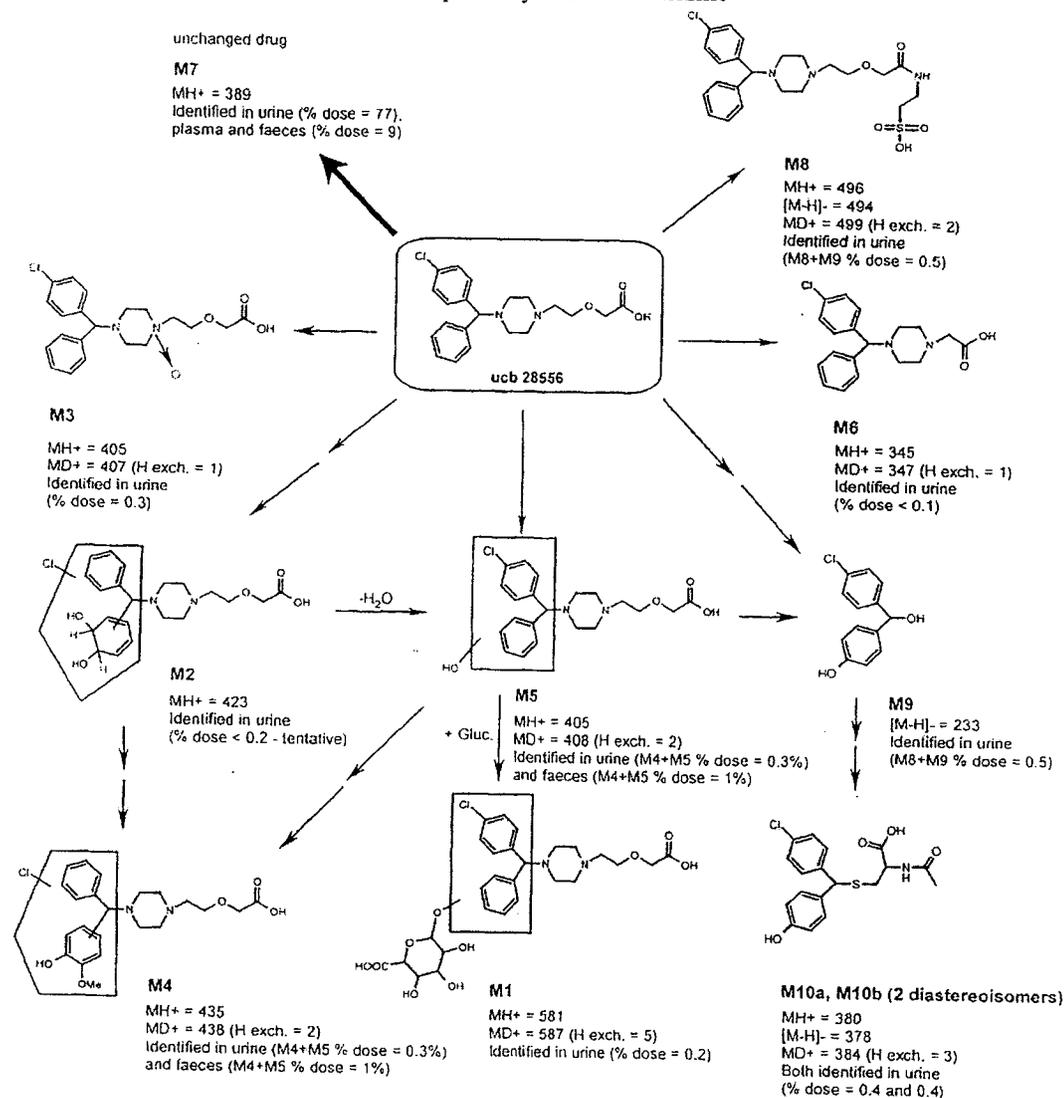
At least 13 minor metabolites have been detected in urine (refer to Figure 1 below) and together represent only 3.5% of the dose at 48 hours. In 48-hour fecal extracts, two radioactive metabolites accounting for approximately 1% of the dose have been detected and identified as hydroxymethoxy- (M4) and as hydroxy-levocetirizine (M5).

In the human radiolabeled mass balance evaluation (study A233), levocetirizine accounted for all measurable radioactivity in plasma, whereas the *O*-dealkylated derivative (P026), the primary human metabolite, could be detected and quantified in plasma in some but not all subjects. Measurable plasma levels of this metabolite were also found in other pharmacokinetic studies. The concentrations of this metabolite, were generally very low after single dose administration ( $C_{\max} = 3$  to 11 ng/mL) and increased, at steady state ( $C_{\max}$  values between 11 and 47 ng/mL) as a result of long half-life exceeding 24 hours. The renal clearance of P026 is extremely low (estimated  $0.67 \pm 0.36$  mL/min).

When incubated *in vitro* with NADPH-fortified human liver microsomes, levocetirizine, cetirizine and the S-enantiomer (ucb 28557) were transformed at a low rate. Phenyl ring hydroxylation, *N*-oxidation and *O*- and *N*-dealkylation reactions were demonstrated. The

*O*- and *N*-dealkylation pathways were primarily mediated by CYP3A4 while phenyl ring hydroxylation appeared to involve multiple and/or unidentified CYP isoforms. Stereoselectivity was observed for some pathways, with the *S*-enantiomer being preferred over levocetirizine as a substrate for the *O*-dealkylation reaction.

**Figure 1.** Proposed human metabolic pathways of levocetirizine

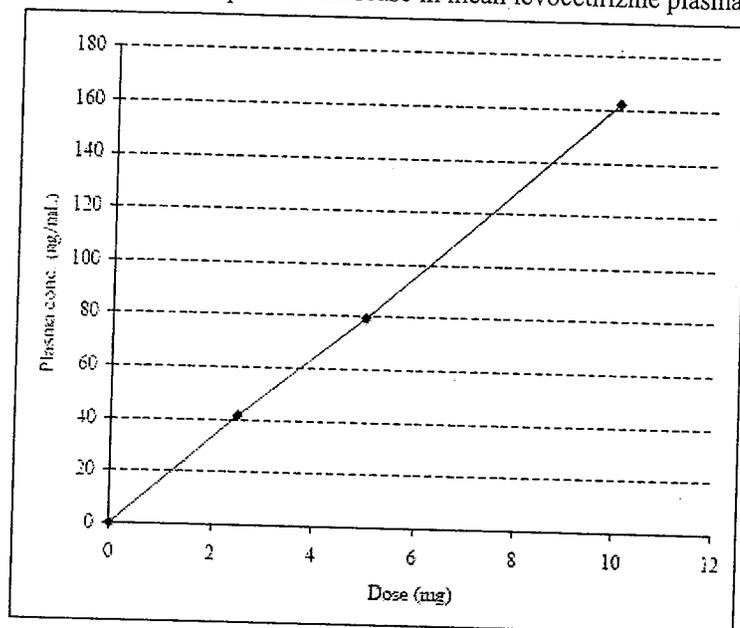


### 2.2.6 Is systemic exposure of levocetirizine proportional to increments of dose following administration of levocetirizine in the dose range of 2.5 to 30 mg?

In cross-study comparisons, exposure to levocetirizine increases proportionally with dose over the dose range studied (5 mg to 30 mg, studies A221, A238, A00263 and A00419) in healthy subjects. Total body clearance, half-life, and relative urinary excretion are all independent of dose. Although complete pharmacokinetic profile has not been determined in target patient population, dose dependent increase in plasma levels was

also observed in patient population with PAR following repeated administration of 2.5 mg to 10 mg (Figure 2 below and Table 3, section 2.2.2 above).

**Figure 2.** Dose dependent increase in mean levocetirizine plasma concentration



### 2.2.7 What are the characteristics of the exposure-response relationship for efficacy?

No thorough PK/PD study has been performed with levocetirizine, however, two studies included both PK and PD assessments: Study A184 which evaluated histamine-induced wheal and flare, and A254 which studied mediator release and cell recruitment in the skin following experimental antigenic stimulation induced using the skin chamber technique and measured plasma and blister fluid concentrations.

No direct PK/PD relationship exists for levocetirizine. The levocetirizine plasma concentrations peaked during the first 2 hours post-dose followed by a rapid decline. The peak pharmacodynamic effects on the other hand are generally observed within 3 to 6 hours and maintained for at least 24 hours post-dose.

As shown in Table 4 below, histamine-induced wheal was inhibited by about 78% at both 4 and 8 hours after a 2.5 mg oral dose of levocetirizine to healthy volunteers (Study A184). The corresponding inhibition of flare was about 85% after the same dose. At these time points, mean plasma levocetirizine concentrations were 78 and 53 ng/mL, respectively. At 24 hours post-dose, adult as well as pediatric patients exhibited significant wheal and flare inhibition exceeding 50% even when the plasma levocetirizine concentrations declined more than 90% from its peak to as low as 20 ng/mL (adults) and 26 ng/mL (children). The pharmacodynamic time-lag observed across various studies was recently documented by the counter clockwise hysteresis loop (Figure 3) plotted by Gillard and co-workers recently presented as an abstract {ACI International 2005; (Suppl

1): 274, ABS. 735. UCB Reference Code ADPE05G1501} to describe the time-course of wheal and flare inhibition and free levocetirizine plasma concentration (Figure 3). It was concluded that levocetirizine is primarily governed by the affinity of the drug for the H<sub>1</sub> receptor and not by the plasma pharmacokinetics of the drug. At 2.5 mg, dextrocetirizine (S-enantiomer) did not exhibit any relevant inhibition of the histamine-induced wheal and flare.

**Table 4.** Plasma Levocetirizine concentration (PK) vs. wheal and flare inhibition (PD) relationship after single oral dose administration of levocetirizine (mean ± SD)

Population	Study No. (Dose)	Time after administration (h)	Plasma/serum concentrations (ng/mL)	Wheal inhibition (%)	Flare inhibition (%)
Healthy adult volunteers <sup>(a)</sup>	A184 (2.5 mg)	4	77.9 ± 15.10	78 ± 27.6	85.0 ± 23.3
		8	53.1 ± 12.29	77.3 ± 15.0	84.5 ± 17.3
Allergic adult volunteers <sup>(a)</sup>	A00373 (5 mg)	12	58.14 ± 13.41	63.22 ± 24.92	78.68 ± 16.47
		24	20.03 ± 8.13	51.52 ± 26.34	68.93 ± 17.65
Children with mild allergic rhinitis <sup>(b)</sup>	IIS study (5 mg) <sup>(c)</sup>	0.5	350 ± 186		
		1	414 ± 132	≈55	
		2	367 ± 108	≈100	≈92
		3	314 ± 99	≈95	≈90
		4	264 ± 83	≈100	≈95
		6	202 ± 73	≈100	≈95
		8	151 ± 56	≈96	≈94
		10	113 ± 47	≈92	
		24	25.8 ± 12.8	≈71	≈90
	26	20.1 ± 11.1	≈55	≈89	
	28	15.7 ± 10.7	≈46	≈87	

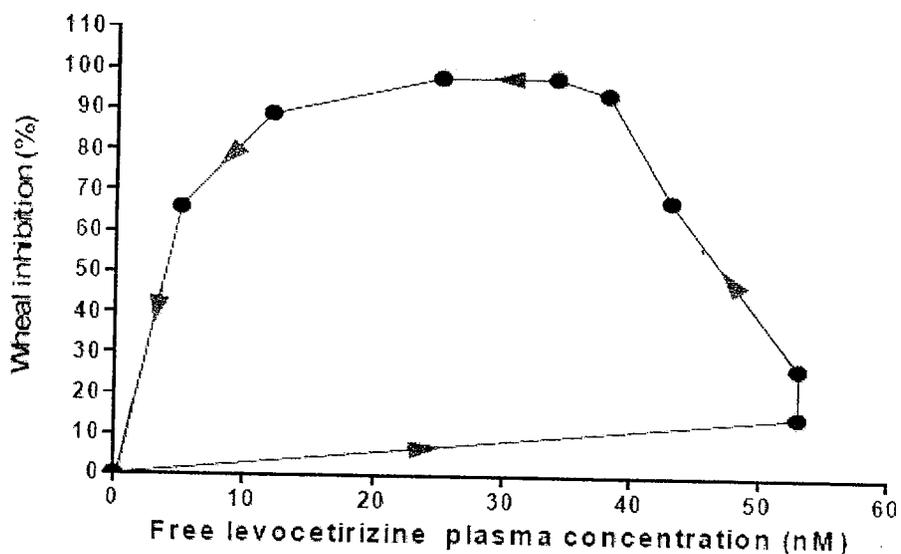
<sup>(a)</sup> Histamine 100 mg/mL

<sup>(b)</sup> Epicutaneous test with histamine phosphate 1 mg/mL

<sup>(c)</sup> Reference # 32

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**Figure 3.** Time-course of histamine induced wheal inhibition plotted against free levocetirizine plasma concentration (reference: Gillard M et al. 2005).



Allergen-induced wheal and flare were also inhibited by about 75% and 85%, respectively, at both 4 and 7 hours after a 5 mg oral dose of levocetirizine to 18 adult allergic volunteers (A00373). At 24 hours, the flare inhibition was still 69%, corresponding to mean plasma concentrations at these time points of only 20 ng/mL (A00373) consistent with the data found in studies described earlier.

### 2.2.7 Does levocetirizine prolong the QTc interval?

In a 5 mg and 30 mg single dose thorough QT study among healthy subjects to assess the possible effect of levocetirizine on the QT/QTc interval, levocetirizine did not appear to prolong the QTc interval in a clinically meaningful way. After baseline and placebo adjustment, the maximum mean QTc change was 3 msec (1-sided 95% upper confidence interval: 7 msec) for the 5 mg dose and -1 msec (1-sided 95% confidence interval: 2 msec) for the 30 mg dose at 4 hours and 24 hours, respectively, following drug administration. Used as a positive control, moxifloxacin (400 mg) had a maximum mean QTc change of 14 msec (1-sided 95% Upper confidence interval: 17 msec) after baseline and placebo adjustment at 4 hours following drug administration. Further details can be found in the QT study (A00419) review by the IRT team dated March 7, 2007.

### 2.2.8 How do the pharmacokinetics and pharmacodynamics in children 6-11 years compare to those in adults?

No levocetirizine pharmacokinetic studies in adolescents (12 to 17 years) and children (6 to 11 years) were submitted as part of this application. A pharmacokinetic study in children 6 to 11 years have been referenced from the literature (Simons FER and Simons KJ: *J Allergy Clin Immunol* 2005; 116:355-61.) and the study results are discussed here.

This published manuscript reported about 2-fold increase in systemic exposure of levocetirizine in children 6 to 11 years compared (cross-study) to adult participants in the pivotal bioequivalence study (Table 1). Consistent with the exposure data, the total body oral clearance in children was found to be about 43% lower compared to adults following oral dosing. The mean time to peak plasma concentration is slightly prolonged in children compared to adults (1.2 vs. 0.86 hr).

**Table 5.** Mean (SD) pharmacokinetic parameters in adults ages  $\geq 18$  years (study A232) and in children ages 6-11 years.

Dose = 5 mg	AUC (ng.hr/mL)	C <sub>max</sub> (ng/mL)	C <sub>24h</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	CL/f (mL/min/kg)	V <sub>d</sub> /f (L/kg)
Adults (18-55 yrs)	1614 (542)	216 (47)	20 ± 10	0.86 (0.42)	7.5 (1.4)	0.63 (0.14) [44]*	0.41 (0.08) [25 L]
Children (6-11 yrs)	3549 (342)	450 (37)	26 ± 13	1.2 (0.72)	5.7 (0.2)	0.82 (0.05) [25]*	0.40 (0.02) [12 L]
Adolescent (12-17 yrs)			74 ± 24*				

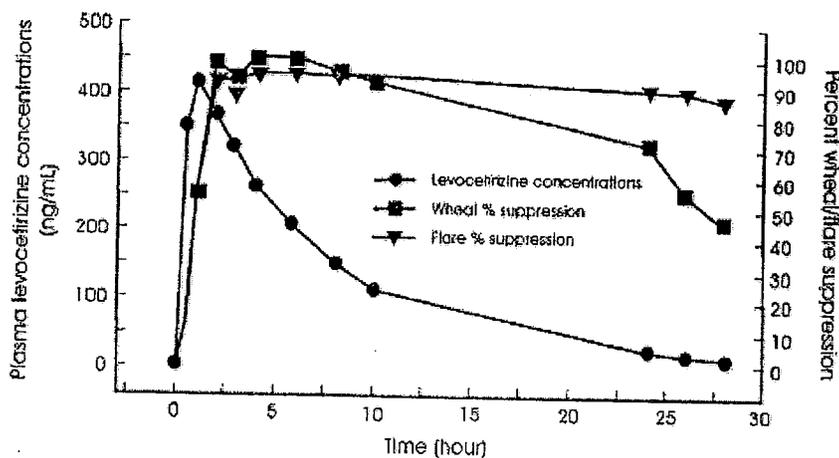
\* expressed as mL/min assuming 30 kg for an average child and 60 kg for an average adult

\*\*C<sub>17h</sub> after 4 weeks of treatment

Reference: Simons FER and Simons KJ: J Allergy Clin Immunol 2005; 116:355-61.

In children 6 to 11 years, levocetirizine was shown to provide significant peripheral antihistaminic activity from 1 to 28 hours after a single dose. As shown in Figure 4, the PD effect initially lags behind plasma levocetirizine concentration but prolongs well past the time of rapidly declining plasma concentration, which is consistent with the counter-clockwise hysteresis loop found in adults for inhibition of histamine-induced wheal.

**Figure 4.** Time course of wheal/flare suppression plotted against levocetirizine plasma concentrations



### 2.3 Intrinsic Factors

The applicant evaluated the effect of several intrinsic factors including age, gender, BMI, 2D6 phenotype on levocetirizine exposure (Table 6). Race was not evaluated as levocetirizine pharmacokinetics has been almost entirely studied in Caucasians.

**Table 6.** Summary (Mean  $\pm$  SD) of plasma pharmacokinetic parameters in adult healthy subjects following administration of single-dose of 5 mg levocetirizine across various intrinsic factors compiled from a number of clinical pharmacology studies (A221, A230, A232, A233 and A238).

Intrinsic Factors (Groups)	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC (ng.h/mL)	T <sub>1/2</sub> (hr)	CL/f (mL/min/kg)	Vz/f (L/kg)
<b>Age</b>							
18-39 yrs	58	303 $\pm$ 54	1.00 $\pm$ 0.45	2602 $\pm$ 831	7.5 $\pm$ 1.6	0.67 $\pm$ 0.14	0.42 $\pm$ 0.07
40-60 yrs	19	298 $\pm$ 99	0.79 $\pm$ 0.40	2710 $\pm$ 844	9.0 $\pm$ 2.4	0.51 $\pm$ 0.07	0.40 $\pm$ 0.10
18-60 yrs	77	301 $\pm$ 67	0.95 $\pm$ 0.45	2629 $\pm$ 830	7.9 $\pm$ 1.9	0.63 $\pm$ 0.14	0.41 $\pm$ 0.08
<b>Gender</b>							
Males	40	311 $\pm$ 78	0.92 $\pm$ 0.47	2878 $\pm$ 736	8.6 $\pm$ 1.8	0.59 $\pm$ 0.12	0.41 $\pm$ 0.10
Females	37	291 $\pm$ 53	0.98 $\pm$ 0.42	2359 $\pm$ 851	7.1 $\pm$ 1.7	0.67 $\pm$ 0.16	0.42 $\pm$ 0.05
<b>BMI</b>							
<25 kg/m <sup>2</sup>	62	304 $\pm$ 63	0.92 $\pm$ 0.42	2581 $\pm$ 660	7.6 $\pm$ 1.7	0.65 $\pm$ 0.14	0.40 $\pm$ 0.07
>25 kg/m <sup>2</sup>	15	293 $\pm$ 84	1.06 $\pm$ 0.56	2826 $\pm$ 1338	8.9 $\pm$ 2.6	0.54 $\pm$ 0.11	0.44 $\pm$ 0.12
<b>CYP2D6 Phenotype</b>							
Poor metabolizer	9	308 $\pm$ 48	1.10 $\pm$ 0.38	2904 $\pm$ 1418	7.1 $\pm$ 1.9	0.68 $\pm$ 0.20	0.32 $\pm$ 0.06
Extensive Metabolizer	63	311 $\pm$ 59	0.91 $\pm$ 0.45	2651 $\pm$ 722	7.7 $\pm$ 1.7	0.63 $\pm$ 0.13	0.41 $\pm$ 0.08

#### 2.3.1 Elderly

Age exhibited a tendency to increase half-life and to decrease oral total body clearance, but, as the PK studies did not include subjects older than 65 years, the effect of age could not be fully characterized. Since the drug is primarily cleared renally, exposure is likely dependent on the impairment of renal function associated with elderly subjects rather than old age.

#### 2.3.2 Pediatric Patients

No pharmacokinetic studies in children (6 to 11 years) and adolescents (12 to 17 years) have been submitted as part of this NDA. A pharmacokinetic study in children 6 to 11 years have been referenced from the literature (Simons FER and Simons KJ: J Allergy Clin Immunol 2005; 116:355-61). Results from this study are described in section 2.2.9.

#### 2.3.3 Gender

Gender appears to have a modest effect on the pharmacokinetics of levocetirizine. There is a tendency for half life to be slightly shorter in women (7.1 hr) than in men (8.6 hr). However, the body weight-adjusted clearance in women (0.7 mL/min/kg) appears to be comparable to that in men (0.6 mL/min/kg).

### 2.3.4 Renal Impairment

Systemic exposure, as evidenced by AUC, exhibited 1.8-, 3.2-, and 4.3-fold increase in mild, moderate and severe renal impaired patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, and 2.9-fold. Renal clearance as well as total body clearance of the unbound drug was progressively reduced with the severity of renal impairment, measuring 88% and 77% reduction in severe renal impaired patients, respectively, compared to healthy subjects. Protein binding was independent of the degree of renal impairment. Systemic exposure of levocetirizine (AUC) increased by 5.7-fold in end-stage renal disease (ESRD) patients compared to subjects with normal renal function. Hemodialysis has minimal effect on the removal of levocetirizine. As a result, no dosage adjustment is needed for subjects during this treatment. The sponsor suggested dose and/or dosing frequency adjustment with differing degrees of renal impairment. Based on the exposure data, this reviewer explored different dosing scenarios for renal impaired patients. The predicted exposure data following repeated dosing based on single-dose kinetics for increasing severity of renal impaired patients is presented in Table 7.

**Table 7.** Exposure prediction for renal impaired patients for sponsor proposed and reviewer recommended dosing scenarios

<i>PK Parameters</i>	<i>Healthy</i>	<i>Mild Impaired</i>	<i>Moderate Impaired</i>	<i>Severe Impaired</i>
$T_{1/2}$ (hr)	10.4	14.9	20.6	29.8
AI	1.25 (QD)	1.5 (QD)	1.8 (QD)	1.24 (once/3d)
AI	1.25 (QD)	1.5 (QD)	1.24 (once/2d)	1.24 (once/3d)
Obs. AUC (ng.hr/mL) (5 mg single-dose)	2213	3885	7000	9582
Pred. AUC (ng.hr/mL) (single-dose)	2213 (5 mg)	1943 (2.5 mg)	3500 (2.5 mg)	4791 (2.5 mg)
Pred. AUC* (ng.hr/mL) (multiple-dose)	2766 (5 mg QD)	5828 (5 mg QD)	6300 (2.5 mg QD)	11882 (5 mg once/3d)
<b>Pred. AUC** (ng.hr/mL) (multiple-dose)</b>	<b>2766 (5 mg QD)</b>	<b>2914 (2.5 mg QD)</b>	<b>4340 (2.5 mg once/2 d)</b>	<b>5940 (2.5 mg once/3 d)</b>

AI = Accumulation Index derived from:  $AI = 1/(1 - e^{-kt})$ , where  $k = 0.693/T_{1/2}$

\* Sponsor suggested dosing; \*\* Reviewer suggested dosing

This reviewer recommended the following dosing scheme that is different from what the sponsor proposed:

Sponsor's dosing proposal: — QD for healthy and mild renal impaired; — for moderate renal impaired; — for severe renal impaired; contraindicated in patients with  $CL_{CR} < 10$  mL/min and ESRD patients.

Reviewer's dosing recommendation: 5 mg QD for healthy; 2.5 mg QD for mild renal impaired; 2.5 mg once every 2 days for moderate renal impaired; 2.5 mg twice weekly, i.e. once every 3 or 4 days for severe renal impaired; contraindicated in patients with  $CL_{CR} < 10$  mL/min and ESRD patients.

### 2.3.5 Hepatic Impairment

The sponsor did not conduct any pharmacokinetic study in hepatic impaired subjects. From study A230 (renal impairment study), the total body non-renal clearance is estimated to be 9.9 mL/min, i.e. constituting about 28% of the total body clearance. Since, majority of the drug is cleared via urine, hepatic clearance constitutes a relatively minor pathway of drug elimination. However, in the absence of a specific study, the effect of hepatic impairment on levocetirizine PK remains undetermined.

## 2.4 Extrinsic Factors

### 2.4.1 What are the extrinsic factors that influence exposure or response?

The applicant formally evaluated the effect of FDA recommended high-fat food on levocetirizine exposure. There were no specific drug-drug interaction studies conducted as part of this application. For most part, reference was made to the drug-drug interaction section of the cetirizine label.

### 2.4.2 What is the effect of food on the bioavailability of levocetirizine and what dosing recommendations should be made regarding administration in relation to meals?

Food has no effect on the extent of levocetirizine exposure ( $AUC_{0-inf}$ ) but the time to peak plasma concentration ( $T_{max}$ ) is delayed by 1.25 hours (from 0.75 to 2 hours) and  $C_{max}$  is decreased by 36% in the presence of high-fat meal. No change in drug exposure with food was further confirmed by the fact that the percentages of unchanged drug excreted in urine after administration of the drug in fed condition (74.4%) or in fasted condition (73.2%) were comparable. Therefore, levocetirizine can be taken without regard to food.

### 2.4.3 Drug-drug Interactions

#### 2.4.3.1 Is levocetirizine a substrate of cytochrome-P450 or any other drug metabolizing enzymes?

The *in vitro* metabolism of levocetirizine was studied alongside that of cetirizine and its S-enantiomer in human liver microsomes. *In vitro*, levocetirizine is poorly metabolized in human liver microsomes. Michaelis-Menten kinetics revealed that the *in vitro* metabolic pathways are characterized by very low affinity and very low intrinsic metabolic clearance values. The metabolites generated included products of phenyl ring hydroxylation, N-dealkylation and N-oxidation, although these pathways were characterized by a very low intrinsic metabolic clearance (0.017-0.206  $\mu\text{L}/\text{min}/\text{mg}$  protein). The N-dealkylation and O-dealkylation pathways were primarily mediated by CYP3A4, while the other pathways involved multiple and/or unidentified enzymes. The principal circulating human metabolite is the O-dealkylated product (P026), which is likely produced by CYP3A4 enzyme. This metabolite is found in dogs.

Levocetirizine is not a substrate of CYP2D6. Pharmacokinetic data was pooled and average summarized in Table 6 from a number of Phase I studies (A221, A232, A233 and A238), where subjects were CYP2D6 phenotyped. The pharmacokinetic parameters, including  $C_{max}$  and AUC, of levocetirizine were comparable in poor (3 males and 6 females) and extensive metabolizers (35 males and 28 females).

#### 2.4.3.2 Is levocetirizine an inhibitor and/or an inducer of CYP or any other drug-metabolizing enzymes?

The potential inhibitory effect of levocetirizine on the activities of model substrates of CYP enzymes 1A2 (Ethoxyresufin 0.4  $\mu$ M), 2C9 (Tolbutamide 100  $\mu$ M), 2C19 (S-Mephenytoin 100  $\mu$ M), 2D6 (Bufuralol 10  $\mu$ M), 2E1 (Chlorzoxazone 100  $\mu$ M), and 3A4 (Testosterone 65  $\mu$ M) was investigated *in vitro* in human liver microsomes. No effects of levocetirizine on the studied markers were observed at a concentration of 100  $\mu$ M i.e. > 100-fold the  $C_{max}$  following oral administration of 5 mg in the clinic. These *in vitro* investigations were conducted with vehicle controls but without any positive controls (known strong inhibitors) for each marker activities. However, the above results coupled with the literature data (Nicolas JM et al. Chem Biol Interact: 1999 Nov 15; 123 (1): 63-79) of no inhibitory effect of cetirizine on any drug-metabolizing P450s, it can be concluded that levocetirizine is not likely to interfere with the P450-mediated metabolic clearance of co-administered drugs. In human hepatocyte *in vitro* study, levocetirizine did not induce marker activities for CYP1A, CYP2C9, CYP3A4 or UGT1A1 at concentrations up to 10  $\mu$ M, which is generally well above the plasma levels of the drug following clinical doses. Within the experimental conditions, positive controls such as 100  $\mu$ M omeprazole caused significant increases in CYP1A2 activity (26-fold) and UGT1A1 activity (2.6-fold), 33  $\mu$ M  $\beta$ -naphthoflavone caused increases in CYP1A2 activity (8.3-fold) and UGT1A1 activity (2.9-fold), and 10  $\mu$ M rifampin caused increases in CYP3A4 activity (16-fold) and CYP2C9 activity (2-fold).

#### 2.4.3.3 Is levocetirizine a substrate and/or inhibitor of P-glycoprotein or any other transporter processes?

The permeability of levocetirizine ~~was~~ was intermediate exhibiting a weak asymmetric transport of the drug with B > A transport greater than A > B transport (efflux ratios between 1.32 and 1.98) indicating the presence of an active transport mechanism. The polarity of the transport was inhibited (81.5%) in the presence of quinidine suggesting that levocetirizine is a weak substrate of P-gp. In Caco-2 cell monolayers, levocetirizine at concentrations up to 100  $\mu$ M does not inhibit the transport of digoxin, a marker substrate for P-gp.

OATP1A2 and OAT4 were found to be capable of moderate levocetirizine uptake. Levocetirizine was not a substrate for transporters known to be involved in hepatobiliary elimination (OATP1B1 and OATP1B3).

## 2.5 General Biopharmaceutics

### 2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Levocetirizine is a highly soluble (94.6 g/100 mL) and a moderately permeable (approximately 86% of radioactivity excreted in urine in a mass balance study) drug that exhibits dose-dependent increase in systemic exposure over the 2.5-30 mg dose range. The permeability of levocetirizine ( $P_{app}$ :  $4.38 \times 10^{-6}$  cm/s) was determined to be intermediate. It is a rapidly dissolving (> 85% within 15 minutes) drug product.

### 2.5.2 What is the comparative bioavailability of the to-be-marketed formulation to the formulation(s) used in the pivotal trials?

The formulation proposed for registration is the same as that used in pivotal clinical trials with the exception of study A222 (pivotal clinical trial) where a heavier tablet allowing blinding with the active comparator was used. The levocetirizine to-be-marketed 5 mg tablet formulation dosed was bioequivalent (in terms of rate and extent of absorption) to the heavier pivotal trial levocetirizine 5 mg tablet. In addition, each test tablet was also bioequivalent to the reference extemporaneous solution at the 5 mg dose strength.

A scoring line allowing for breaking the tablet in two halves (each approximately 2.5 mg) is present on the tablet proposed for registration in the United States. *In vitro* multi-media (pH 1, 4.5, 6.5, water) comparative dissolution tests indicated that at least 85% of the labeled amount is released within the first 15 minutes for both test and reference products, therefore the profile comparison with an *f2* test was considered unnecessary by the sponsor. It was concluded that the scoring line has no impact on the dissolution profile of the drug.

It was demonstrated on three batches that breaking the 5 mg levocetirizine tablets actually results in two equivalent halves with a very reproducible weight (RSD between 3.3% and 5.6%) and a high accuracy (half tablet weights were equivalent and represented effectively about 50% of the unbroken tablet weight) and, therefore, a very close content of active ingredient. The dissolution profile of 2 halves of a tablet is equivalent to that of an unbroken tablet, i.e., the deterioration of the film of the tablet at the scoring site has no impact on the dissolution. These data, taken together, demonstrate that the 5 mg proposed commercial tablet can be halved to enable a 2.5 mg dose with no formulation impact other than that observed for the unbroken tablet.

### 2.5.3 What is the composition of the to-be-marketed formulation?

The quantitative composition of the 5 mg levocetirizine (available in one strength only) is described below (Table 8). All inactive ingredients used in the manufacture of levocetirizine dihydrochloride 5 mg tablets meet compendial requirements, \_\_\_\_\_

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**Table 8.** Composition of the 5 mg levocetirizine to-be-marketed tablet

	Component	5 mg levocetirizine dihydrochloride tablet
Core	Levocetirizine dihydrochloride	5.00
	Microcrystalline cellulose	/
	Colloidal anhydrous silica	
	Lactose monohydrate	
	Magnesium stearate	
Coating		

## 2.6 Analytical Section

### Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

An overview of the bioanalytical methods employed in PK, PD and efficacy studies is presented in Table 9. Levocetirizine and its *O*-dealkylated metabolite (P026) have generally been measured in plasma and urine by achiral validated methods. Although, according to this reviewer, some chiral interconversion may happen, there is no evidence to suggest any significant chiral interconversion taking place *in vivo*. Therefore, the use of achiral chromatography in clinical studies of levocetirizine can be justified. In studies including the racemate, chiral validated HPLC methods were used. Two chiral assays with different sensitivity were developed: one for plasma (lower limit of quantitation for both enantiomers = 20 ng/mL) and one for urine (lower limit of quantitation for both enantiomers = 100 ng/mL), both based on HPLC with UV detection. According to the sponsor, a third, more sensitive chiral assay was also developed for plasma with a lower limit of quantitation of 3 ng/mL for both enantiomers based on LC/ESI/MS, which was used to analyze samples from a 6-month efficacy study (A00264) in PAR patients and samples from an investigator-initiated pediatric pharmacokinetic study (Simons FER and Simons KJ: J Allergy Clin Immunol 2005; 116:355-61). However, plasma concentration data from study A00264 could not be located in the package. In addition, Simons and Simons 2005 reported that the lower limit of quantitation of levocetirizine used in the pediatric study was 12 ng/mL and not 3 ng/mL as claimed by the sponsor in the application. Nevertheless, majority of the plasma concentration data from this pediatric

study were found to be several times the assay limit, hence the bioanalytical data reported for children 6-11 years in the published literature should be reliable.

**Table 9.** Overview of bioanalytical methods used in the PK studies

Laboratory (Country)	Analytical Method	Validation Report	Analytical Report	LOQ (Linear Range) (ng/mL)	Accuracy / Precision	Study(ies) Analyzed
<b>Chiral Method / Plasma</b>						
UCB S.A. Pharma Sector (Belgium)	HPLC / UV	RRLE93H3101	RRLE98D0701	20 (20 - 1000)	> 90% < 10%	A221
<b>Chiral Method / Urine</b>						
UCB S.A. Pharma Sector (Belgium)	HPLC / UV	RRLE93M2101	RRLE98D0701	100 (100 - 1000)	> 91% < 11%	A221
<b>Achiral Methods / Plasma</b>						
UCB S.A. Pharma Sector (Belgium)	HPLC	RRLE92M1401	RRLE93A1102	10 (10 - 800)	> 92% < 10%	A184
SGS Biopharma, S.A. (Belgium)	LC/MS-MS	RRLE98G0701	TA0447	2 (2 - 500)	> 89% < 10%	A234
			ARLE00K1607			A263
			ARLE02A1505			A297
			RRCE02L1905			A00318
SGS Bio-Pharma, SA (Belgium)	LC/MS-MS	RRLE98G0701	RRCE98K0101 (BA/97/242)	20 (20 - 500)	> 89% < 10%	A230
	LC/MS-MS	RRLE98G0701	RRCE98L2305	2 (20 - 500)		A238
SGS Biopharma, S.A. (Belgium)	LC/MS/MS	RRLE98G0701	RRCE98L2303	2 (2 - 500)	> 89% < 10%	A232
<b>Achiral Methods / Urine</b>						
UCB S.A. Pharma Sector (Belgium)	HPLC / UV	RRLE92D1303	RRLE93A1102	50 (50 - 600)	> 99% < 3%	A184
SGS Bio-Pharma SA. (Belgium)	HPLC / UV	RRLE94L1501	RRCE98K0101 (94/156)	50 (50 - 5000)	> 92% < 8%	A230
SGS Bio-Pharma SA. (Belgium)	HPLC / UV	RRLE94L1501	RRCE98L2303	50 (50 - 5000)	> 92% < 8%	A232

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## 4.2. Individual Reports

### Study A238

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**OPEN, RANDOMIZED, STUDY TO DETERMINE THE FOOD EFFECT ON ORAL BIOAVAILABILITY OF UCB 28556 (5 mg TABLET) AFTER SINGLE ADMINISTRATION, AND TO MEASURE THE PHARMACOKINETIC PARAMETERS OF UCB 28556 (5 mg TABLET) AT STEADY-STATE, AFTER REPEATED ADMINISTRATION FOR 8 DAYS, IN NORMAL HEALTHY MALE AND FEMALE VOLUNTEERS UNDER FASTING CONDITION**

**Protocol No:** RPCE97L2404  
**Date of Final Report:** 25 January 2000  
**Phase:** I

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#### **OBJECTIVE**

The objectives of the study were to assess the influence of food on the absorption of ucb 28556 (levocetirizine), and to assess the pharmacokinetic parameters of levocetirizine, in steady state condition, following once daily administration.

#### **STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single center study, divided into two parts:

**Part 1:** Open randomized two-way cross over design in which 20 healthy (10 males and 10 females) subjects received a single oral dose of 5 mg levocetirizine under fasting and fed conditions. The two periods were separated by a 7-day interval period.

**Part 2:** Open, repeated dose design in which 20 healthy (10 males and 10 females) volunteers received repeated oral doses of 5 mg/day levocetirizine for 8 days in fasting conditions.

The same 20 volunteers participated in the two parts of the study, and the two parts were separated by a 3-day interval period.

#### **SUBJECTS**

This study enrolled 21 healthy subjects, aged 18-55 years, of which 20 completed the study and 1 withdrew consent after single dose administration of the study drug without any safety concern(s).

#### **TREATMENT**

Levocetirizine 5 mg tablet (batch number 1107, November 1998)

#### **PHARMACOKINETIC MEASUREMENTS**

Plasma samples were used for time course of concentrations of unchanged drug and of its metabolite ucb P026.

Samples were collected at the following times after the morning dose administrations of Day 1, Day 8 and Day 18:0 (pre-dose), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 9.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after intake, and at the following times after each morning dose administrations from Day 11 to Day 17:0 (pre-dose) 1.5 hours after intake.

#### **Analytical method**

Analysis of study samples for levocetirizine and ucb P026 concentrations were performed by \_\_\_\_\_, using an achiral LC/MS/MS validated method previously developed by \_\_\_\_\_

## **PHARMACOKINETIC RESULTS**

### **Plasma Pharmacokinetics**

#### **Food Effect and Multiple-dose**

The mean (SD) plasma and urine pharmacokinetic parameters following administration of single and multiple-dose of levocetirizine were presented in Table 10. After single dose oral administration of levocetirizine under fasted conditions, peak plasma concentrations of levocetirizine were observed between 0.5 and 2 hours while in the presence of high fat meal, maximal plasma concentrations were observed between 0.75 and 4 hours in most subjects. The median  $T_{max}$  was prolonged from 0.75 to 2 hr under fed condition as compared to fasted condition. The mean  $C_{max}$  and  $AUC_{0-inf}$  were 36% and 14% lower, respectively after a high fat meal compared to fasted state. Although 90% confidence interval was within 80-125% range for lack-of-effect, all subjects exhibited lower AUC value under fed condition compared to fasted condition. The amount of unchanged drug excreted in urine over 48 hours post-dose was calculated to be 3.66 mg (73% of the dose) and 3.72 mg (74% of the dose) under fasted and fed conditions, respectively. Plasma terminal half-life ( $t_{1/2}$ ) was also comparable between the two treatments.  $C_{max}$  and AUC values between males and females, after a single dose, either in fed or in fasted conditions, were comparable.

Mean pre-dose plasma concentrations from Day 12 to Day 17 were generally comparable (21 - 27 ng/mL), thus indicating that the steady-state was reached at 24 hours after the first dose of the multiple-dose treatment. Except for one subject who exhibited rather high pre-dose concentration of 103 ng/mL on day 18, all other subjects measured pre-dose concentrations on Day 18 ranging from 10 to 54 ng/mL. The maximal plasma concentrations measured on Day 18 (mean of 307.6 ng/mL ranging between 175 ng/mL and 401 ng/mL) were observed between 0.5 and 2 hours with a median  $t_{max}$  of 0.75 hrs (Table 10). The mean  $AUC_{0-24h}$  and  $AUC_{0-inf}$  were 2124.2 ng.hr/mL and 2476.5 ng.hr/mL, respectively. Based on  $C_{max}$  and AUC, the accumulation is minimal (10-14%) following repeated administration. Based on the amount of unchanged drug collected over 48 hours post-dose in urine, the accumulation appears to be slightly greater (~ 24%), which is consistent with the drug's terminal half-life of 7-8 hrs)

**Table 10.** Mean (SD) pharmacokinetic parameters of levocetirizine after single-dose (SD) administration under fasted and fed conditions and after multiple-dose (MD) administration of 5 mcg levocetirizine tablet for 8 days

PK Parameters	Treatments			Ratio (Fed/Fasted)	Accumulation Ratio (MD/SD)
	Fed SD	Fasted SD	Fasted MD		
$C_{max}$ (ng/mL)	175.0 (36.8)	269.7 (47.0)	307.7 (60.9)	0.64* (0.6, 0.7)	1.14
$T_{max}^a$ (hr)	2 (0.75, 6)	0.75 (0.5, 2)	0.75 (0.5, 2)		–
$AUC_{0-24h}$ (ng.hr/mL)	1639.2 (354.2)	1944.6 (389.3)	2124.2 (691.7)		1.10
$AUC_{0-t}$ (ng.hr/mL)	1846.9 (485.0)	2157.5 (514.7)	–	0.85* (0.83, 0.88)	–
$AUC_{0-inf}$ (ng.hr/mL)	1899.8 (522.3)	2203.9 (542.4)	2476.5 (1067.5)	0.86* (0.83, 0.89)	1.12
$T_{1/2}$ (hr)	7.8 (1.7)	7.5 (1.4)	8.2 (2.0)		–
$A_{e(0-48h)}$ (mg)	3.72 (0.45)	3.66 (0.49)	4.53 (1.77)	1.02**	1.24

<sup>a</sup> median (range)

\* ratio of geometric means (90% confidence interval)

\*\* ratio of arithmetic means

The metabolite (ucb P026) started to appear in plasma generally 2 hours or later; its concentrations were sustained up to 48 hrs but were much lower than the parent drug (peak plasma concentration ranging from 3 to 7 ng/mL).

Measurable pre-dose plasma ucb P026 concentrations were found on the first day of multiple dose session in 8 out of 20 subjects, thus indicating that plasma concentrations of the metabolite were not returned to the baseline levels in these subjects. From Day 11 to Day 16, plasma concentrations of the metabolite increased slowly and steady-state appeared to have reached on Day 17. Taken together, these results indicate that the terminal half-life of the metabolite is quite long, which might have been at least 24 hours. On Day 18, average  $C_{min}$  of ucb P026 was 16 ng/mL, ranging from 7 to 43 ng/mL. The average multiple-dose peak plasma concentration of 20 ng/mL (ranging 11 to 47 ng/mL) was observed between 0 and 16 hours post-dose. The mean  $AUC_{0-24h}$  was 406 ng.h/mL. The  $AUC_{0-24h}$  metabolite/parent estimate was 19%.

There is one subject — #16), who exhibited markedly greater exposure of the parent as well as metabolite after both single and multiple-dose administration.

## REVIEWER'S COMMENTS AND CONCLUSIONS

Food reduced mean  $C_{max}$  of levocetirizine by 36% and prolonged median  $T_{max}$  from 0.75 hour to 2 hour. The extent of absorption, as evidenced by mean  $AUC_{0-inf}$ , decreased by 14% in the presence of food, i.e. it remained relatively unchanged as the 90% confidence interval (0.83-0.89) was included in the pre-specified criterion for lack-of-effect. This was further confirmed by the fact that the percentages of unchanged drug excreted in urine after administration of the drug in fed condition (74.4%) or in fasted condition (73.2%) were comparable.

Following repeated dose administration, the accumulation of levocetirizine was found to be minimal (10-14%), based on  $C_{max}$  and AUC. However, based on the amount of unchanged drug collected over 48 hours post-dose in urine, the accumulation appears to be slightly greater (~ 24%). The results indicate that, on average, the accumulation of the drug is consistent with the terminal half-life of the drug estimated from single-dose kinetics, suggesting linear pharmacokinetics following multiple-dose administration.

The metabolite (P026) exhibited rather long half-life exceeding 24 hrs that resulted in significant accumulation, which constituted about 19% relative exposure (AUC) compared to the parent drug following chronic administration.

In this study, there was one subject — 16), who consistently demonstrated markedly higher plasma concentration than the rest of the 19 subjects. Systemic exposure ( $AUC_{0-inf}$ ) in this subject was about 2-fold higher than the average of the other 19 subjects under both fasted and fed conditions. After repeated dose administration, exposure values of the parent drug and the metabolite (P026) were found to be even greater, about 2.6-fold and 2.9-fold compared to the mean for the other 19 subjects. Other studies in the submission need to be carefully reviewed to identify such cases of increased exposure of the parent drug and its metabolites, if any. The reason for such high exposure remains undetermined.

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## Study A221

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### **OPEN, RANDOMIZED, TWO-WAY CROSS-OVER STUDY TO COMPARE THE ORAL DISPOSITION OF UCB 28556 WHEN GIVEN ALONE (10 MG) OR AS THE RACEMATE (CETIRIZINE.2HCL 20 MG) AS A SINGLE DOSE OF AN EXTEMPORANEOUS SOLUTION IN HEALTHY VOLUNTEERS UNDER FASTING CONDITIONS**

**Protocol No:** RPCE96B1301  
**Date of Final Report:** 18 MAY 1999  
**Phase:** I

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#### **OBJECTIVE**

The primary objective of this study was to compare the disposition of ucb 28556 (levocetirizine) following single oral administration when given alone (10 mg) or as the racemate (20 mg), both given as an oral extemporaneous aqueous solution.

#### **STUDY DESIGN AND TREATMENT ADMINISTRATION**

The study was performed in a randomized, two-way cross-over, single-dose design with a wash-out phase of 7 days between the two periods.

#### **SUBJECTS**

A total of 12 healthy male and 12 healthy female subjects who were between the ages of 20 and 55 years [mean (sd) of 35.0 (9.5) years], were enrolled and completed the study. All subjects were Caucasians, 22 of them are fast metabolizers and 2 out of 24 (# 004 and #016) were CYP2D6 poor metabolizers.

#### **TREATMENTS**

Treatment 1: oral extemporaneous solution in water containing 10 mg of levocetirizine.

Treatment 2: oral extemporaneous solution in water containing 20 mg of the cetirizine.2HCl.

Treatment 3 (phenotyping): sparteine capsule containing 100 mg of sparteine.

In order to determine the CYP2D6 phenotypic status (poor or extensive metabolizer), subjects were administered with sparteine.

#### **PHARMACOKINETIC MEASUREMENTS**

Plasma samples were collected at 0h (pre-dose), 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 9h, 12h, 16h, 24h, 36h and 48h postdose.

Urine was collected during the following intervals:

0 (pre-dose), 0-3, 3-6, 6-9, 9-12, 12-24, 24-36, and 36-48 hours post-dose.

#### **Analytical method**

Levocetirizine and ucb 28557 (dextrocetirizine) in plasma and urine were assayed by UCB S.A. Pharma Sector, Laboratory of Drug Metabolism and Pharmacokinetics, using a

validated chiral method.

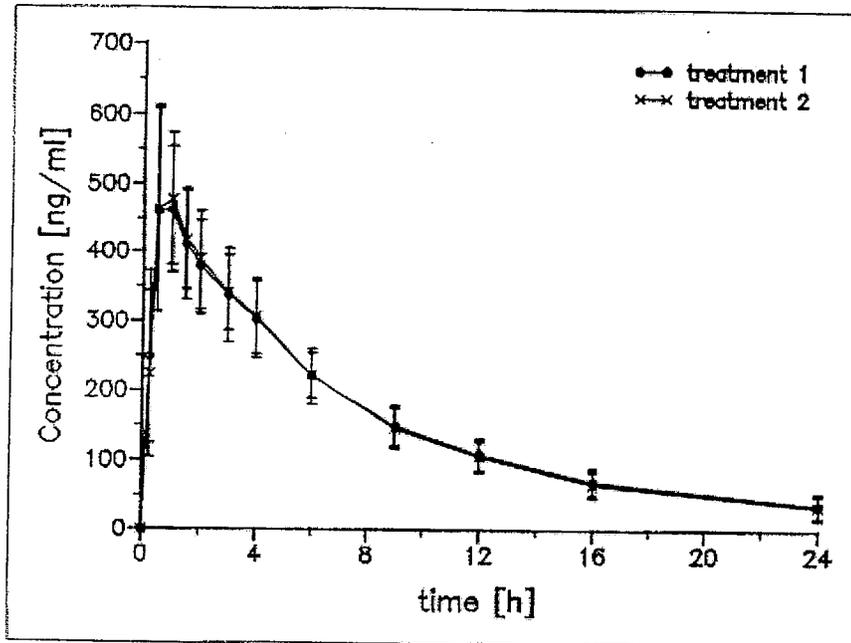
## PHARMACOKINETIC RESULTS

### Plasma Pharmacokinetics

#### Levocetirizine 10 mg vs. Cetirizine 20 mg (Figure 5, Table 11)

Plasma-concentration time plots (Figure 5) of levocetirizine following single-dose administration of 10 mg of Levocetirizine and 20 mg of Cetirizine in 24 healthy subjects were essentially superimposable. The ratios as well as the 90% confidence intervals of rate and extent of absorption of levocetirizine from the two treatments were contained within the 80-125% limits of lack of significant difference (Table 11).

**Figure 5.** Mean (SD) plasma concentrations of levocetirizine following single-dose administration of 10 mg of Levocetirizine (treatment 1) and 20 mg of Cetirizine (treatment 2) in 24 healthy subjects



**Table 11.** Statistical comparisons of levocetirizine pharmacokinetic parameters following single-dose administration of oral solutions of 10 mg Levocetirizine and 20 mg Cetirizine.

	Ae mg	AUC h*ng/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h
Statistic	ANOVA	ANOVA	ANOVA	nonparam.
Transform.	ln	ln	ln	no
Geom. mean (min - max)				Median
Treatment 1	6.74 (4.8-8.7)	4072.5 (2828.6-5654.1)	501.4 (294-709)	0.5 (0.5-1.5)
Treatment 2	7.15 (5.5-10.1)	4043.9 (3175.5-5444.6)	499.1 (331-698)	1.0 (0.5-1.5)
ratio [%]	94.1	100.7	100.4	100
90% CI	89.6 99.0	97.1 104.5	95.6 105.5	75 100
Treatment 1:	oral extemporaneous solution in water containing 10 mg of ucb 28556			
Treatment 2:	oral extemporaneous solution in water containing 20 mg cetirizine.2HCl			

The extent of exposure for levocetirizine was slightly greater in females than in males, as evidenced by C<sub>max</sub> and AUC values that were greater for females (Table 12). These differences are probably related to differences in body weight between females (mean 58.9 kg) and males (mean 75.7 kg). Similarly, the cumulative amount of levocetirizine excreted unchanged in urine in males and females demonstrated the same trend, with greater amount seen in females compared to males (Table 13). These differences could be observed for both treatments and for both levocetirizine and dextrocetirizine.

**Table 12.** Plasma pharmacokinetic parameters of levocetirizine following single-dose administration of oral solutions of 10 mg levocetirizine and 20 mg cetirizine by gender

Parameter	Treatment 1		Treatment 2	
	male (N = 12)	female (N = 12)	male (N = 12)	female (N = 12)
	geomean	geomean	geomean	geomean
AUC <sub>0-1</sub> [h*ng/ml]	3462.7	3871.9	3441.0	3811.4
AUC <sub>0-48</sub> [h*ng/ml]	3676.8	4112.1	3696.5	4011.2
AUC [h*ng/ml]	3910.0	4241.7	3924.7	4166.8
C <sub>max</sub> [ng/ml]	456.03	551.19	449.67	554.05
t <sub>max</sub> [h] Median	0.5	1.0	0.75	1.0
λ <sub>z</sub> [1/h]	0.0836	0.0995	0.0800	0.1048
t <sub>1/2</sub> [h]	8.2910	6.9668	8.6635	6.6120
CL/f [ml/min]	42.626	39.293	42.466	39.999
V <sub>z</sub> /f [l]	30.592	23.696	31.847	22.893

**Table 13.** Urine pharmacokinetic parameters of levocetirizine following single-dose administration of 10 mg levocetirizine oral solution by gender

Parameter	Treatment 1		Treatment 2	
	male (N=12)	female (N=12)	male (N=12)	female (N=12)
Ae [ $\mu$ g]	6624.7	6995.9	6996.4	7523.2
Fe [%]	66.25	69.96	69.96	75.23
CL <sub>R</sub> [ml/min]	30.75	28.80	32.01	31.94

**Chiral Inversion *in vivo*:**

After administration of Levocetirizine, none of the plasma samples assayed contained a quantifiable concentration of S-enantiomer. One urine sample (0-3h) for subject# 16 detected dextrocetirizine (R-isomer) concentration of 0.109 mcg/mL following administration of levocetirizine (S-isomer). The volume of urine collected for this 0-3h sample was 106 mL, which is considerably low compared to an average of 750 mL collected for this time period from the other 23 subjects. This was also reflected in the estimation of levocetirizine in the same sample, which was calculated to be 21.2 mcg/mL; in contrast the majority of the samples from other subjects had levocetirizine concentration in the range of 1-5 mcg/mL. The total amount of levocetirizine collected in the 0-3h time period was comparable to the average amount collected for all other subjects in the 0-3h time period. The lower limit of quantitation of the analytical method used for urine assay was 100 ng/mL, which is insensitive compared to other clinical pharmacology studies (50 ng/mL) in this program. Several urine samples from 20 out of 24 subjects detected the S-isomer of cetirizine (dextrocetirizine), however these samples were not reliably measurable as they were all below the LLOQ of 100 ng/mL. These data confirm the presence of dextrocetirizine in urine following dosing with the single enantiomer (levocetirizine). The source of dextrocetirizine could be \_\_\_\_\_ 2) conversion of levocetirizine (R-form) to the S-form. In this case, based on the data presented, the reviewer is of the opinion that chiral inversion of R-cetirizine (levocetirizine) to the S-form (dextrocetirizine) can not be completely ruled out.

**REVIEWER'S COMMENTS AND CONCLUSIONS**

The present study demonstrated equivalent disposition of levocetirizine following single dose oral administration when given alone (10 mg) or as racemate (20 mg), both given as an oral extemporaneous aqueous solution. The 90% confidence intervals for the treatment ratios of log-transformed C<sub>max</sub>, AUC and A<sub>e</sub> were all within the 80- 125% equivalent range. This conclusion of equivalent exposure of levocetirizine between the two treatments is independent of gender effects. Males exhibited a slightly higher systemic exposure of levocetirizine compared to females following administration of both levocetirizine and cetirizine, which is likely due to the relatively higher dose received by females than males when expressed as mg/kg.

There was not sufficient evidence presented to rule out the possibility of chiral inversion of levocetirizine to the dextro-form.

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## Study A233

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### THE EXCRETION AND PLASMA KINETICS OF TOTAL RADIOACTIVITY IN MAN FOLLOWING A SINGLE ORAL ADMINISTRATION OF [<sup>14</sup>C]-UCB 28556, 5 MG IN A GELATIN CAPSULE: AN OPEN STUDY IN HEALTHY VOLUNTEERS

Protocol No: RPCE97K0101 – Amt 1: 08/12/97 – Amt 2: 06/1 1/98  
Date of Final Report: 17 MARCH 2000  
Phase: I

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#### OBJECTIVE

The primary objective of this study was to define the absorption and excretion kinetics of levocetirizine and its metabolites in man following a single-dose oral administration of 5 mg [<sup>14</sup>C]-levocetirizine to healthy male subjects. In addition, metabolic profiling and determination of the structure of metabolites was performed in urine, feces and plasma.

#### STUDY DESIGN AND TREATMENT ADMINISTRATION

Each subject received a single oral dose of 5 mg of levocetirizine in a gelatin capsule with a target radioactive dose of 46 pCi per subject.

#### SUBJECTS

A total of 4 healthy male subjects who were between the ages of 31 and 46 years were enrolled and completed the study. Subject height and weight ranged from 164-184 cm and 66-85 kg, respectively. All subjects were extensive metabolizers of Debrisoquine (CYP2D6).

#### PHARMACOKINETIC MEASUREMENTS

Blood samples were collected at the following times: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 168 h post dose. A portion of blood (~1 mL) was immediately transferred to a dry lithium heparin tube for the determination of radioactivity in whole blood and remaining blood separately processed to obtain plasma.

Urine was collected during the following intervals: Pre-dose, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-156 and 156-168 h post dose.

Urine collected at 144-156 h (0-12 h after Debrisoquine administration) was subsampled (2 x 20 ml) and the remaining sample combined with the 156-168 h sample to give a 144-168 h sample for total radioactivity analysis.

Feces were collected at 24 h intervals after dose administration as follows: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h post dose. Excreta samples were analyzed daily (where possible) and the subjects were discharged from the clinic 168 h post dose at which time >90% of the administered radioactivity had been recovered.

### Analytical method

*In Vitro* plasma protein binding was determined in pre-dose plasma samples taken from the study subjects. Plasma samples were spiked with labeled and non-labeled levocetirizine, analyzed by liquid scintillation counting (LSC) for percent recovery.

*Ex vivo* plasma protein binding was determined in post-dose plasma samples collected at 1, 6 and 24h, percent recovery being calculated using LSC.

### RESULTS

*In vitro* protein binding results indicated high plasma protein binding of the drug, approximately 95% at levocetirizine concentrations ranging from 0.2 to 1 mcg/mL. The *ex vivo* plasma protein binding results indicated high levels of protein binding of levocetirizine occurring with a mean of 96.1%, 91.7%, and 87.3% at 1, 6 and 24 hrs post dose, respectively, further confirming the *in vitro* results.

Plasma and whole blood pharmacokinetic parameters are presented in Table 14. The whole blood concentrations of total radioactivity paralleled plasma total radioactivity patterns, though at a lower level. The mean terminal half-life estimates of total radioactivity in whole blood and plasma were 6.8 and 10.7 hrs, respectively. The individual whole blood : plasma ratio of total radioactivity during the first 12 h ranged between 0.56-0.62, 0.53-0.68, 0.53-0.65 and 0.51-0.65 for subjects 1, 2, 3 and 4, respectively, which suggests that the radio-labeled components were only minimally associated with blood cells.

**Table 14.**

Pharmacokinetic Parameters of Total Radioactivity in Plasma and Whole Blood

Sample	Subject	C <sub>max</sub> (µg equiv.ml <sup>-1</sup> )	T <sub>max</sub> (h)	Elimination Half-life (h)	AUC (0-1 h) (µg equiv.h.ml <sup>-1</sup> )	AUC (0-∞) (µg equiv.h.ml <sup>-1</sup> )
Plasma	1	0.221	1.5	11.53	2.34	3.11
	2	0.305	0.5	10.01	2.50	3.12
	3	0.311	0.5	10.75	2.41	3.11
	4	0.248	0.5	10.35	1.98	2.51
	Mean ± SD	0.272 ± 0.044	0.75 ± 0.50	10.66 ± 0.66	2.31 ± 0.23	2.96 ± 0.30

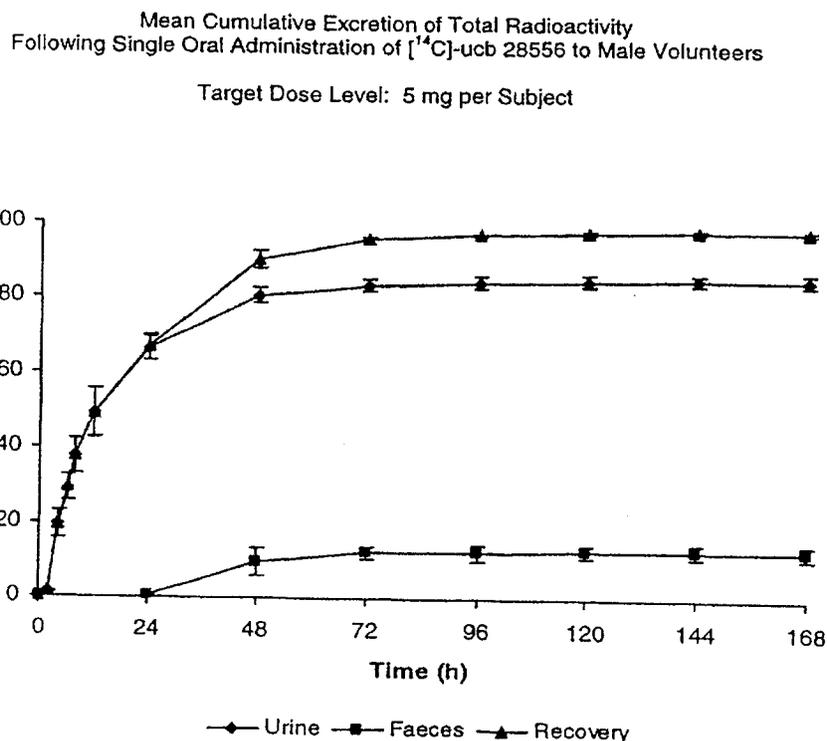
Sample	Subject	C <sub>max</sub> (µg equiv.g <sup>-1</sup> )	T <sub>max</sub> (h)	Elimination Half-life (h)	AUC (0-1 h) (µg equiv.h.g <sup>-1</sup> )	AUC (0-∞) (µg equiv.h.g <sup>-1</sup> )
Whole Blood	1	0.138	1.5	8.74	0.82	1.51
	2	0.185	0.5	6.23	1.10	1.48
	3	0.189	0.5	6.19	1.01	1.37
	4	0.159	0.5	6.17	0.84	1.13
	Mean ± SD	0.170 ± 0.027	0.75 ± 0.50	6.83 ± 1.27	0.97 ± 0.11	1.37 ± 0.17

t (AUC 0-1 h) = 24 for plasma and 12 for whole blood

The cumulative excretion of total radioactivity following oral administration of [<sup>14</sup>C]-ucb 28556 (levocetirizine) is presented graphically in Figure 6. The recovery of radioactivity was ranging from 97.8% - 98.7% with mean of 98.3% by 168 h post-dose. The major route of recovery was *via* the urine, accounting for 84.1-87.7% (mean of 85.5%) of the total administered radioactive dose while recovery in the feces accounted for only 10.4-

14.5% (mean of 12.9%). Total recovery of radioactivity in the excreta was near complete by 120 h post-dose with a mean of 97.8% (97.4-98.0).

Figure 6.



### Metabolite profiling

The proposed metabolic pathways of levocetirizine in humans are shown in Figure 7 below. The metabolism of levocetirizine was found to occur formally by five initial pathways: direct conjugation with taurine, cleavage of the ether bond, N-oxide formation, aromatic oxidation and N-dealkylation at the piperazinyl/benzhydryl nitrogen-carbon bond.

In plasma, unchanged levocetirizine accounted for all measurable radioactivity.

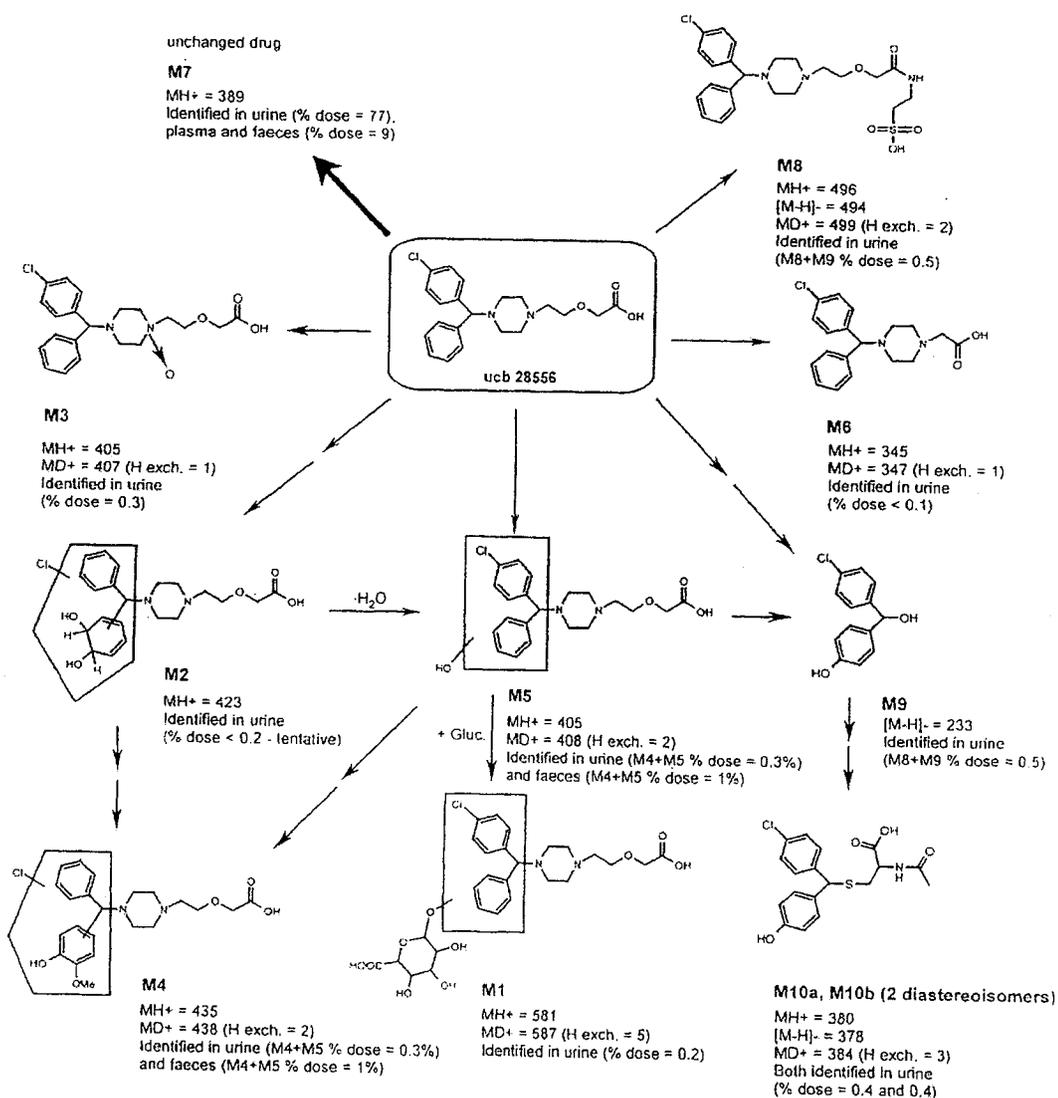
Unchanged levocetirizine constituted, on average, about 77% of the radioactive dose while at least 13 minor radioactive metabolites made up another 3.5% of the dose in urine collected over 48 hours post-dose. Other unidentified metabolites in urine represented about 1.5% of the dose.

Similarly, in feces, the major component detected was unchanged levocetirizine. Up to 9% of the dose was excreted unchanged during 48 h post-dose. Two radioactive metabolites constituted another 1% of the dose in feces.

The total amount of radioactivity excreted in urine and feces following oral administration were 90.3% of the dose over 48 hours post-dose, out of which the parent drug and the metabolites constituted 85.8% and 4.5%, respectively.

Therefore, the major route of elimination of levocetirizine was found to be urinary excretion of unchanged drug, constituting about 77% of the dose over 48 hrs. Fecal elimination was a minor route. However, similar to urine, unchanged drug comprised of the majority of the drug-related materials in feces, amounting to 8.5% of the dose. Metabolites of levocetirizine constituted 3.5% and 1% of the dose in urine and feces, respectively over the same time interval of 48 hours post-administration.

**Figure 7.** Proposed metabolic pathways of levocetirizine in man.



## REVIEWER'S COMMENTS AND CONCLUSIONS

*In vitro* and *ex vivo* protein binding results indicated high plasma protein binding of the drug ( $\geq 90\%$ ). Drug and its metabolites were found to be minimally associated with blood cells, mostly residing in circulating plasma. The mass balance study was well conducted, reporting near complete recovery of 98% of the dose in urine and feces. The major route of elimination was identified to be urine (86% of the dose); feces constituted a minor route (13% of the dose). Majority of the drug was found to be eliminated unchanged in urine and feces, comprising 77% and 9% of the dose, respectively over 48 hours post administration. Metabolites constitute only about 4.5% and 1% in urine and feces, respectively in the same time period. Therefore, metabolism contributes very little towards overall disposition of the drug.

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## Study A232

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**OPEN, RANDOMIZED, THREE WAY CROSS-OVER SINGLE DOSE STUDY TO COMPARE ORAL BIOAVAILABILITY OF TWO FORMULATIONS OF ucb 28556 (5 MG TABLET USED IN CLINICAL TRIALS, 5 MG TABLET PROPOSED FOR MARKETING AUTHORIZATION PURPOSE), TO A 5 MG EXTEMPORANEOUS SOLUTION OF ucb 28556, IN NORMAL HEALTHY MALE AND FEMALE VOLUNTEERS UNDER FASTING CONDITION**

Protocol No: RPCE97J1001/R 98.1841  
Date of Final Report: 25 NOV 1999  
Phase: I

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### **OBJECTIVE**

The aim of the study was to compare the oral bioavailability of two formulations of ucb 28556 (levocetirizine): the 5 mg relatively heavier tablet used in the pivotal clinical trial (study no. A222) and the 5 mg to-be-marketed unscored tablet used in all other clinical trials. An extemporaneous solution of levocetirizine dosed at 5 mg was used as the reference formulation. Each tablet was compared with each other and also with the reference formulation.

### **STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single centre study with an open randomized three-way crossover design in which subjects received a single oral dose of 5 mg levocetirizine in each treatment period separated by a minimum washout of 7 days.

### **SUBJECTS**

Twenty-four (24) healthy subjects (12 males and 12 females) between the ages 20-55 years entered and completed the study, out of which 23 were extensive metabolizers of dextromethorphan (CYP2D6) and one was identified as being a poor metabolizer. Subject height and weight ranged from 163-186 cm and 53.6-89.4 kg, respectively.

### **PHARMACOKINETIC MEASUREMENTS**

Plasma samples were collected after each treatment at the following times: pre dose (0), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36 and 48h post-dose.

Urine was collected after each treatment during the following intervals: 0-3h, 3-6h, 6-9h, 9-12h, 12-16h, 16-24h, 24-36h, 36-48h post dose.

### **Analytical method**

The validated ranges of sample quantitation for plasma and urine were 2 to 500 ng/mL and 50 to 5000 ng/mL, respectively. During the validation in plasma, at the lower limit of quantification (2 ng/mL), the between run precision (CV%) was less than 10% and

accuracy was better than 89%.

In urine, at the lower limit of quantification (50 ng/mL), the between run precision (CV%) was less than 8% and accuracy was better than 108%. For both plasma and urine, the precision and accuracy were well below the  $\pm 20\%$  requirement for a validated bioanalytical method.

Accuracy and precision of the bioanalytical method for levocetirizine during the plasma sample analyses were demonstrated using quality control samples at low (4 ng/mL), medium (40 ng/mL) and high (400 ng/mL) concentrations for levocetirizine and are tabulated in Table 15. The same data for urine at low (80 ng/mL), medium (800 ng/mL) and high (4000 ng/mL) concentrations for levocetirizine were listed in Table 15. For both matrices, these results meet the regulatory criterion [refer to the guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy.

**Table 15.** Accuracy and precision of QC samples during sample analyses

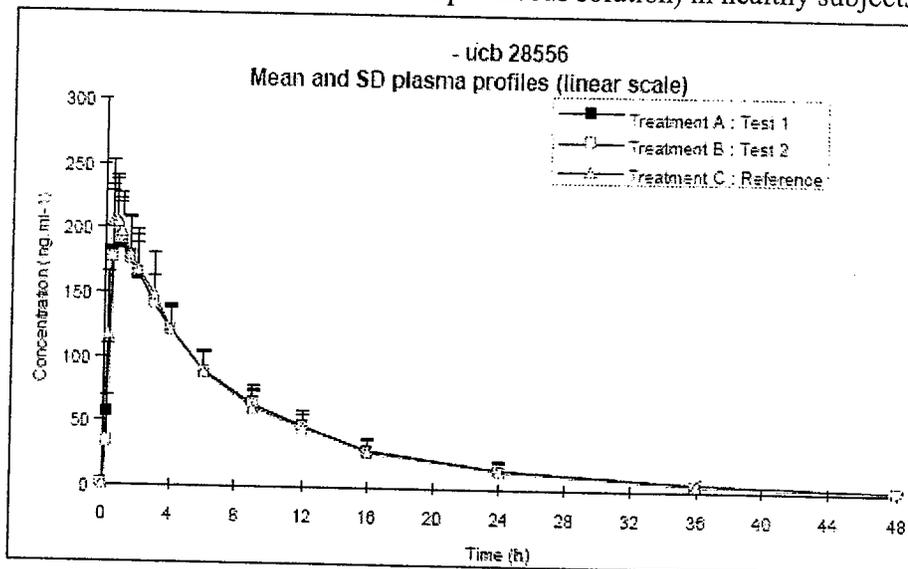
<b>Plasma</b>	<b>Quality Control Samples</b>		
	<b>4 ng/mL</b>	<b>40 ng/mL</b>	<b>400 ng/mL</b>
Precision (%CV)	12.0	7.9	5.7
Accuracy(% deviation)	+3.4	+4.8	-5.3
<b>Urine</b>	<b>80 ng/mL</b>	<b>800 ng/mL</b>	<b>4000 ng/mL</b>
Precision (%CV)	16.1	5.2	3.9
Accuracy(% deviation)	+1.1	-2.2	+1.2

## RESULTS

Plasma concentration vs. time profiles (mean  $\pm$  SD) of levocetirizine following single-dose oral administration of three different formulations of 5 mg levocetirizine (ucb 28556) were nearly superimposable (Figure 8). Mean (SD) pharmacokinetic parameters of levocetirizine are presented in Table 16.

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**Figure 8.** Plasma concentration vs. time profile (mean  $\pm$  SD) of levocetirizine following single-dose oral administration of three different formulations of 5 mg levocetirizine (ucb 28556) (Treatment A: tablet used in pivotal trial A222, Treatment B: to-be-marketed unscored tablet, Treatment C: extemporaneous solution) in healthy subjects.



Following single dose administration of 5 mg levocetirizine in healthy subjects, the peak plasma concentrations as well as area under the concentration-time curves of levocetirizine were not significantly different between the three treatments (Table 16). The ratio with the 90% confidence interval calculated for  $C_{max}$  for the comparison of Treatment A (clinical tablet) vs. Treatment B (to-be-marketed tablet), was 1.01 (0.96-1.05) that is well within the bioequivalence range of 0.80-1.25. The times to reach peak plasma concentrations ( $T_{max}$ ) were comparable between treatments as the median values ranged between 0.5 and 0.75 h.

For  $AUC_{0-t}$ , the ratio with the 90% confidence interval for Treatment A (clinical tablet) vs. Treatment B (to-be-marketed tablet), was 1.02 (0.99-1.06) that is also well within the bioequivalence range of 0.80-1.25. The same holds true for  $AUC$ , i.e. the ratio with 90% confidence interval for Treatment A vs. Treatment B was 1.02 (0.99-1.05). Refer to Table 16 for other comparative ratios and 90% confidence intervals: Treatment A vs. Treatment C and Treatment B vs. Treatment C.

For each treatment, the estimates of terminal half-life were identical, i.e. 7 hours.

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**Table 16.** Pharmacokinetic parameters and statistical results of levocetirizine (ucb 28556) following single-dose oral administration of three different formulations of 5 mg levocetirizine (ucb 28556) (Treatment A: tablet used in pivotal trial A222, Treatment B: to-be-marketed tablet, Treatment C: extemporaneous solution) in healthy subjects.

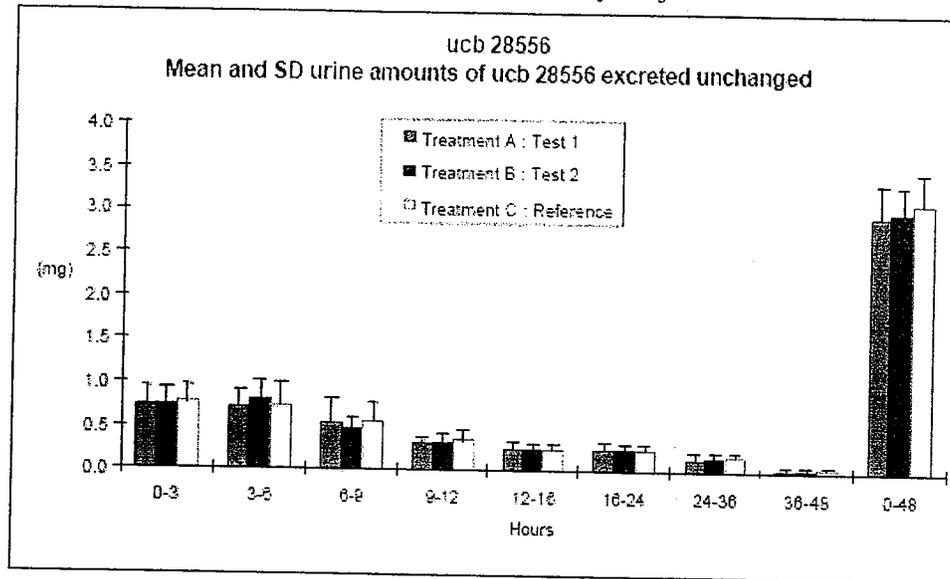
Ucb 28556 (N=24)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (h)	AUC <sub>0-t</sub> (ng/ml.h)	AUC (ng/ml.h)	C <sub>max</sub> /AUC
<b>Treatment A : (Test 1)</b>					
Mean	217.08	-	1842.26	1688.88	0.131
S.D.	33.11	-	303.49	314.98	0.024
Median	221.50	0.75	1591.42	1622.20	0.129
<b>Treatment B : (Test 2)</b>					
Mean	215.60	-	1813.74	1661.54	0.134
S.D.	33.42	-	343.79	357.22	0.029
Median	210.00	0.75	1581.32	1641.57	0.131
<b>Treatment C : (Reference)</b>					
Mean	221.79	-	1856.54	1701.53	0.134
S.D.	40.98	-	344.17	357.21	0.028
Median	217.50	0.50	1825.17	1652.83	0.138
<b>Statistics</b>	NS (1)		NS (1)	NS (1)	NS (1)
A-C		NS (2)			
B-C		NS (2)			
A-B		NS (2)			
<b>ER (90% CI)</b>					
A-C	0.98, (0.94-1.03)	0.125, (0.00-0.25)*	0.99, (0.96-1.03)	0.99, (0.96-1.03)	0.99, (0.94-1.04)
B-C	0.98, (0.93-1.02)	0.125, (0.00-0.25)*	0.97, (0.94-1.00)	0.97, (0.94-1.01)	1.00, (0.95-1.05)
A-B	1.01, (0.96-1.05)	0.0, (-0.125-0.125)*	1.02, (0.99-1.05)	1.02, (0.99-1.05)	0.99, (0.94-1.04)

ER: estimated ratio of geometric means; NS: no significant difference (p>0.05); \* : Non-parametric 90% CI (1): ANOVA (PROC GLM) on log-transformed data; (2): Non-parametric Wilcoxon analysis

Mean (SD) amount of levocetirizine excreted in urine are presented in Figure 9. The data suggested that the amount of unchanged levocetirizine excreted at each sampling post-dose time interval was found to be comparable between the three treatments. About 59%, 60% and 62% of the dose was excreted unchanged in urine 48 hours after administration of levocetirizine. The mean renal clearance was 1807 mL/hr after treatment A, 1889 mL/hr after treatment B and 1905 mL/hr after treatment C.

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**Figure 9.** Urinary excretion amounts of levocetirizine (ucb 28556) following single-dose oral administration of three different formulations of 5 mg levocetirizine (ucb 28556) (Treatment A: tablet used in pivotal trial A222, Treatment B: to-be-marketed tablet, Treatment C: extemporaneous solution) in healthy subjects.



#### REVIEWER'S COMMENTS AND CONCLUSIONS

The levocetirizine to-be-marketed 5 mg tablet formulation dosed was bioequivalent (in terms of rate and extent of absorption) to the heavier levocetirizine tablet dosed at 5 mg used in the pivotal clinical study (Study A222). Moreover, each test tablet was bioequivalent to the reference extemporaneous solution at the 5 mg dose strength.

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## Study A230

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### **OPEN-LABEL, NOT RANDOMISED, MULTICENTRE, SINGLE DOSE PHARMACOKINETICS STUDY OF 5 MG OF UCB 28556, ORALLY ADMINISTERED IN SUBJECTS WITH NORMAL RENAL FUNCTION OR WITH DIFFERENT DEGREES OF RENAL FUNCTION IMPAIRMENT**

Protocol No: RPCE97E2801  
Date of Final Report: 15 MAR 1999  
Phase: I

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#### **OBJECTIVE**

To assess the single dose pharmacokinetics, safety and tolerability of 5 mg tablet of ucb 28556 (levocetirizine) administered orally in 6 healthy subjects with normal renal function, 6 subjects with mild renal impairment, 3 subjects with moderate renal impairment, and 3 subjects with severe renal impairment in order to evaluate the relationship between pharmacokinetic parameters and the degree of renal impairment (creatinine clearance).

#### **STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a multi-centre study with an open randomized three-way crossover design in which subjects received a single oral dose of 5 mg levocetirizine in each treatment period separated by a minimum washout of 7 days.

#### **SUBJECTS**

Eighteen (18) subjects (6 males and 12 females) between the ages 46-73 years entered and completed the study. Based on sponsor categorization, 6 were healthy with normal renal function ( $CL_{CR} \geq 90$  mL/min), 6 were patients with mild renal impairment ( $CL_{CR} \geq 45 - < 90$  mL/min) and 6 were patients with moderate renal impairment ( $CL_{CR} \geq 10 - < 45$  mL/min). This categorization did not follow the FDA recommended categorization of renal function groups (refer to Guidance for industry (May 1998): Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling). After taking a closer look at the individual subject creatinine clearance data, this reviewer determined that there were 3 subjects in the moderate renal impaired group, who should have been classified as severe renal impaired subjects based on the above guidance. Therefore, in this study, there were 6 healthy subjects with normal renal function ( $CL_{CR} > 80$  mL/min), 6 with mild renal impairment ( $CL_{CR} = 50-80$  mL/min), 3 with moderate renal impairment ( $CL_{CR} = 50-80$  mL/min), and 3 with severe renal impairment ( $CL_{CR} < 30$  mL/min). Subject height and weight ranged from 153-183 cm and 56.0-93.3 kg, respectively.

#### **PHARMACOKINETIC MEASUREMENTS**

Plasma samples were collected pre-dose (0) and 0.5, 1, 2, 4, 6, 8, 10, 14, 24, 30, 36, 48 and 60 h post-dose. For renal impaired patients, additional plasma samples were drawn at 72, 84 and 96 h post-dose.

Urine was collected after treatment during the following intervals: 0-4h, 4-8h, 8-14h, 14-24h, 24-48h, 48-72h post dose. For renal impaired patients, additional fraction of 72-96h was also collected.

### **Analytical method**

Levocetirizine (ucb 28856) and the metabolite (ucb P026) concentration levels were determined in all available plasma samples using a validated LC/MS method. In urine, levocetirizine concentration levels were determined using a validated HPLC/UV method.

The validated ranges of sample quantitation were 2 to 500 ng/mL for levocetirizine in plasma, 2 to 250 ng/mL for P026 (levocetirizine metabolite) in plasma and 50 to 5000 ng/mL for levocetirizine in urine. During the validation in plasma, at the lower limit of quantitation (2 ng/mL), the between run precision (CV%) was less than 10% and accuracy was better than 89%.

In urine, at the lower limit of quantification (50 ng/mL), the between run precision (CV%) was less than 8% and accuracy was better than 108%. For both plasma and urine, the precision and accuracy were well below the  $\pm 20\%$  requirement for a validated bioanalytical method.

Accuracy and precision of the bioanalytical method for levocetirizine during the plasma sample analyses were demonstrated using quality control samples at low (4 ng/mL), medium (40 ng/mL) and high (400 ng/mL) concentrations for levocetirizine and are tabulated in Table 17. The same data for urine at low (80 ng/mL), medium (800 ng/mL) and high (4000 ng/mL) concentrations for levocetirizine were listed in Table 17. For both matrices, these results meet the regulatory criterion [refer to the guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy.

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**Table 17.** Summary data for precision (%CV) and accuracy (% deviation) of quality control samples during sample analysis

	Quality Control Samples		
<b>ucb 28856 Plasma</b>	<b>4 ng/mL</b>	<b>40 ng/mL</b>	<b>400 ng/mL</b>
Precision (%CV)	10.4	6.7	9.1
Accuracy(% deviation)	+6.6	-0.6	-1.3
<b>P026 Plasma</b>	<b>3 ng/mL</b>	<b>30 ng/mL</b>	<b>400 ng/mL</b>
Precision (%CV)	7.1	10.1	11.6
Accuracy(% deviation)	+3.4	-1.7	-4.7
<b>ucb 28556 Urine</b>	<b>80 ng/mL</b>	<b>800 ng/mL</b>	<b>4000 ng/mL</b>
Precision (%CV)	8.6	3.5	4.6
Accuracy(% deviation)	-3.9	-1.4	+0.5

## RESULTS

The pharmacokinetic parameters of levocetizine and its major metabolite P026 following single-dose oral administration of 5 mg levocetizine (ucb 28856) in healthy subjects and patients with mild, moderate and severe renal impairment are summarized in Table 18 below.

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**Table 18.** Plasma and urine pharmacokinetic parameters of ucb 28556 (levocetirizine) and its metabolite P026 following single-dose oral administration of 5 mg ucb 28556 (levocetirizine) in healthy and renal impaired subjects (mild, moderate, and severe).

	Healthy	Mild Impaired	Moderate Impaired	Severe Impaired	Ratio: Mild/Hlthy	Ratio: Mod/Hlthy	Ratio: Sev/Hlthy
<b>Baseline <math>CL_{CR}</math> (mL/min)</b>	98.2 (7.2)	62.4 (9.8)	34.8 (4.3)	18 (5.8)	0.64	0.35	0.18
<b>Plasma PK Parameters of Levocetirizine (ucb 28556)</b>							
<b><math>C_{max}</math> (ng/mL)</b>	220.5 (68.8)	295.2 (60.8)	322.3 (16.7)	317.7 (104.6)	1.34	1.46	1.44
<b><math>T_{max}</math> (hr)<sup>s</sup></b>	1	1	1	1	NC	NC	NC
<b><math>AUC_t</math> (ng*hr/mL)</b>	2160.0 (288.7)	3827.3 (766.5)	6693.0 (1841.5)	8429.7 (3612.5)	1.77	3.10	3.90
<b>AUC (ng*hr/mL)</b>	2212.5 (282.7)	3884.5 (769.6)	6999.7 (2077.6)	9582.0 (4904.4)	1.76	3.16	4.33
<b><math>T_{1/2}</math> (hr)</b>	10.4 (2.8)	14.9 (3.1)	20.6 (6.3)	29.8 (11.5)	1.44	1.98	2.87
<b><math>CL/f</math> (mL/min)</b>	35.5 (5.5)	21.0 (3.7)	13.6 (3.7)	10.1 (4.1)	0.59	0.38	0.28
<b><math>CLu/f</math> (mL/min)</b>	360.1 (67.3)	224.2 (38.2)	144.8 (37.9)	96.9 (42.1)	0.62	0.40	0.27
<b>Plasma PK Parameters of metabolite (P026)</b>							
<b><math>C_{max}</math> (ng/mL)</b>	4.2 (0.7)	5.0 (1.1)	12.2 (3.5)	14.1 (10.5)	1.17	2.89	2.57
<b><math>T_{max}</math> (hr)<sup>s</sup></b>	29.9	33.0	48.1	30.0			
<b><math>AUC_t</math> (ng*hr/mL)</b>	166.4 (66.8)	311.2 (152.7)	883.0 (258.5)	821.0 (253.5)	1.87	5.31	4.93
<b><math>AUC_t</math> ratio% (P026/28556)</b>	7.7	8.1	13.2	9.7			

<sup>s</sup> median; NC = No change

Following single dose administration of 5 mg levocetirizine, the peak plasma concentration ( $C_{max}$ ) of levocetirizine was about 34-46 % higher in subjects with differing degrees of renal impairment than in healthy subjects with normal renal function, while time to peak concentration ( $T_{max}$ ) values were similar between healthy and all three renal impaired groups. Compared to the healthy subjects, AUC was 1.8, 3.2, and 4.3-fold higher in the mild, moderate, and severe renal impaired subjects, respectively.

The disposition of levocetirizine was altered in subjects with renal impairment when compared to healthy subjects. Compared to the healthy subjects, total systemic clearance (unbound) was reduced in subjects with impaired renal function by 38% in mild, 60% in moderate, and 73% in severe renal impairment. The magnitude of the reduction was significantly correlated ( $r^2=0.81$ ) to the reduction in creatinine clearance ( $CL_{CR}$ ). The terminal half-life ( $T_{1/2}$ ) of levocetirizine was prolonged 1.4, 2.0, and 2.9-fold in subjects with mild, moderate, and severe renal impairment, respectively.

Protein binding of levocetirizine was not affected by the severity of renal impairment. Individual subject *ex vivo* protein binding data ranged from 87.7 to 91.6% across the four groups.

Metabolite P026 was detected even up to the last sampling time point, i.e. 96 h post-dose for 17/18 subjects. In one of the subjects with mild renal impairment (subject no. 312), P026 concentrations in plasma were all below the level of quantitation. The plasma P026 data revealed that the elimination phase was yet to be reached at the end of the collection period (96 h post-dose) for most subjects, therefore the elimination half-life values were not estimated. The  $C_{max}$  was marginally higher (17%) in the mild renal impaired subjects, while in moderate to severe renal impaired patients, the magnitude of increase was found to be significantly higher (2.6 to 2.9 fold) compared to healthy subjects. The  $T_{max}$  values ranged from 14 to 36 h (median value = 30 h), from 30 to 48 h (median value = 33 h), from 30 to 60 h (median value = 48 h), and from 30 to 72 (median value = 30 h) in healthy subjects, mild, moderate, and severe impaired subjects, respectively. Like  $C_{max}$ , the  $AUC_t$  showed a similar pattern of increase with severity of renal impairment, exhibiting 1.9-fold increase in mild renal impaired patients, and approximately 5-fold increase in moderate and severe renal impaired patients. On average, the metabolite/parent drug ratio increased marginally in renal impaired patients compared to healthy subjects (7.7% in healthy vs. 8.1-13.2% in renal impaired patients).

The amount of parent drug excreted unchanged (levocetirizine) in urine declined with the severity of impairment; about 70%, 66%, 36%, and 28% of the drug was recovered unchanged in the urine of healthy, mild, moderate, and severe renal impaired subjects, respectively (Table 19). In all 3 subjects with severe renal impairment (subject nos. 121, 221 and 322) and 1 out of 3 subjects (subject no. 122) with moderate renal impairment, excretion of levocetirizine was not complete even after the last sampling time point (96 h post-dose) as sizeable amounts of levocetirizine were still detected in urine. The renal clearance of levocetirizine, corrected for protein binding, accounted for a mean (SD) of 260 (55) mL/min in healthy subjects. This value indicated that levocetirizine was partially excreted by active tubular secretion. The unbound renal clearance ( $CL_{RU}$ ) was reduced by 42%, 78%, and 88% in mild, moderate, and severe renal impaired patients, respectively. The magnitude of this decrease was related to the reduction in  $CL_{CR}$  ( $r^2=0.81$ , see Table 20). The non-renal clearance of levocetirizine, corrected for protein binding, was 28% in healthy subjects, 33% in mild renal impaired subjects, and then increased up to 63% and 69% in subjects with moderate and severe renal impairment, respectively.

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**Table 19.** Urine pharmacokinetic parameters of ucb 28556 (levocetirizine) following single-dose oral administration of 5 mg ucb 28556 (levocetirizine) in healthy and renal impaired subjects (mild, moderate, and severe).

	Healthy	Mild Impaired	Moderate Impaired	Severe Impaired	Ratio: Mild/Hlthy	Ratio: Mod/Hlthy	Ratio: Sev/Hlthy
Baseline $CL_{CR}$ (mL/min)	98.2 (7.2)	62.4 (9.8)	34.8 (4.3)	18 (5.8)	0.64	0.35	0.18
$CL/f$ (mL/min)	35.5 (5.5)	21.0 (3.7)	13.6 (3.7)	10.1 (4.1)	0.59	0.38	0.28
Urine PK Parameters of Levocetirizine (ucb 28556)							
$CL_R$ (mL/min)	25.6 (4.6)	14.3 (5.1)	5.3 (2.9)	3.1 (1.2)	0.56	0.21	0.12
$CL_{RU}$ (mL/min)	259.6 (54.6)	151.3 (49.4)	56.7 (31.0)	30.2 (12.5)	0.58	0.22	0.12
$CL_{NRU}$	100.6 (29.5)	72.9 (41.6)	88.1 (7.4)	66.7 (29.6)	0.73	0.88	0.66
Ae (mcg)	3521.0 (284.7)	3301.8 (918.1)	1793.7 (594.4)	1413.0 (68.5)	0.94	0.51	0.40
$CL_{NRU}/CL_U$	27.9 (6.2)	33.0 (18.5)	62.8 (11.4)	68.6 (0.8)	1.18	2.25	2.46
$f_c$ (%)	70.4 (5.7)	66.0 (18.3)	35.9 (11.9)	28.2 (1.4)	0.94	0.51	0.40

<sup>s</sup> median; NC = No change

**Table 20.** Summary of linear regression analysis of main urine levocetirizine PK parameters against baseline creatinine clearance.

Parameter	Intercept	Slope	95%CI on slope	r <sup>2</sup>	p(1)	p(2)
$CL_R$ (mL/min/1.73m <sup>2</sup> )	-3.10	+0.29	+0.22 ; +0.35	0.83	< 0.01	0.18
$CL_{RU}$ (mL/min/1.73m <sup>2</sup> )	-27.6	+2.9	+2.13 ; +3.61	0.81	< 0.01	0.27
$CL_{NRU}$ (mL/min/1.73m <sup>2</sup> )	+62.4	+0.34	-0.19 ; +0.84	0.11	0.19	< 0.01

r<sup>2</sup>: Pearson determination coefficient; p(1) probability associated with the hypothesis of no linear correlation; p(2) probability associated with the hypothesis of intercept different of zero (see Statistical printouts in Table 10.a-c (Section 16.1.9)).

Subject no. 121 in the severe renal impairment group exhibited  $C_{max}$ , AUC and  $T_{1/2}$  values markedly higher (nearly 2-fold) than values observed in the other 2 subjects of this group while the total amount excreted unchanged in urine over 96 h post-dose in this subject was comparatively similar to the other 2 subjects. This subject exhibited the lowest baseline  $CL_{CR}$  value of 11.7 mL/min of the group of severe renal impairment, compared to 19.5 and 22.9 mL/min, respectively in other 2 subjects, which might explain the dramatic increase in exposure in this subject.

Results of regression analysis performed between plasma levocetirizine pharmacokinetic parameters and baseline creatinine clearance are summarized in Table 21. A strong linear relationship was observed between  $CL/f$ , AUC,  $CL_U/f$ , AUC<sub>U</sub> and  $T_{1/2}$  versus baseline  $CL_{CR}$  ( $r^2 > 0.66$ ,  $p < 0.01$ ).

**Table 21.** Summary of linear regression analysis of main plasma levocetirizine PK parameters against baseline creatinine clearance

Parameter	Intercept	Slope	95% CI on slope	r <sup>2</sup>	p(1)	p(2)
<b>ucb 28556</b>						
C <sub>max</sub> (ng/ml)	370.5	-1.47	-2.48 ; -0.47	0.38	< 0.01	< 0.01
AUC (ng.h/ml)	10241	-87.4	-119.3 ; -55.4	0.68	< 0.01	< 0.01
CL <sub>uf</sub> (ml/min/1.73m <sup>2</sup> )	2.90	+0.32	+0.25 ; +0.39	0.85	< 0.01	0.24
t <sub>1/2</sub> (h)	30.7	-0.22	-0.31 ; -0.14	0.66	< 0.01	< 0.01
C <sub>max,u</sub> (ng/ml)	36.7	-0.15	-0.26 ; -0.04	0.34	0.01	< 0.01
AUC <sub>u</sub> (ng.h/ml)	1039	-9.1	-12.9 ; -5.3	0.62	< 0.01	< 0.01
CL <sub>u,f</sub> (ml/min/1.73m <sup>2</sup> )	34.8	+3.21	+2.39 ; +4.03	0.81	< 0.01	0.21

r<sup>2</sup> : Pearson determination coefficient; p(1) probability associated with the hypothesis of no linear correlation; p(2) probability associated with the hypothesis of intercept different of zero (see Statistical printouts in Tables 9.a-i (Section 16.1.9)).

## REVIEWER'S COMMENTS AND CONCLUSIONS

This study enrolled 18 subjects with the intention of enrolling 6 healthy subjects and 6 each in mild and moderate renal impaired groups. Creatinine clearance values were used to group subjects with differing degrees of renal impairment; however the grouping was not done based on FDA recommended classification. Following FDA's categorization, the moderate group was found to include 3 subjects with severe renal impairment. Therefore, this reviewer re-summarized the PK data of the originally assigned moderate group of 6 patients to include 3 in the moderate group and 3 in the severe group.

This study revealed a significant correlation between systemic clearance of unchanged levocetirizine and creatinine clearance, indicating that kidneys play a major role in the overall elimination of the drug. The total body clearance of the unbound drug was progressively reduced with the severity of renal impairment, measuring 38%, 60%, and 77% reduction in mild, moderate, and severe renally impaired patients, respectively, compared to healthy subjects. This resulted in a concomitant increase in systemic exposure, as evidenced by AUC, of 1.8-, 3.2-, and 4.3-fold increase in mild, moderate and severe renal impaired patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, and 2.9-fold compared to subjects with normal renal function. Renal clearance of the unbound drug also exhibited progressive decline with the severity of renal impairment, measuring up to 88% reduction in severe renal impaired patients compared to healthy subjects. Protein binding was independent of the degree of renal impairment.

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## Study A234

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### **OPEN-LABEL, NOT RANDOMISED, MONOCENTRE, SINGLE DOSE PHARMACOKINETIC STUDY OF 5 MG OF UCB 28556, ORALLY ADMINISTERED IN SUBJECTS WITH END-STAGE RENAL DISEASE (ESRD) UNDERGOING HAEMODIALYSIS**

**Protocol No:** RPCE97K1301  
**Date of Final Report:** NOV 1999  
**Phase:** I

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#### **OBJECTIVE**

The objectives of the study are as follows: 1) To examine the dialysability and the hemodialysis clearance of 5 mg of levocetirizine and its metabolite ucb P026. 2) To examine the plasma pharmacokinetics of levocetirizine and of its metabolite ucb P026 after single oral administration, and the corresponding clearance pattern in subjects with end-stage renal disease (ESRD) undergoing hemodialysis.

#### **STUDY DESIGN AND TREATMENT ADMINISTRATION**

This was a single-center, single dose, open-label study in 5 anuric hemodialysed male or female subjects, undergoing dialysis three times a week since at least one month, aged 18-80 yrs, and with end-stage renal disease (ESRD). Each subject underwent a 4-hour dialysis session just before the study drug (5 mg levocetirizine) administration and from 44 to 48 hours post-dose (high-flux polysulfone membrane from 1.1 to 1.8 m<sup>2</sup>, dialysate flow = 500 ml/min, blood flow between 179 and 250 ml/min).

#### **SUBJECTS**

Five (5) subjects (3 males and 2 females) between the ages 39-78 years were enrolled and completed the study. Subject height and weight ranged from 154-173 cm and 49.5-75.0 kg, respectively. Four of the subjects were Caucasians and one was Black. Two were smokers, three moderately consumed alcohol, all consumed tea or coffee.

#### **BLOOD SAMPLING**

The blood samples were taken pre-dose (0min), 30min, 1h, 2h, 4h, 10h, 24h, 32h, 44h, 44h 15min, 44h 30min, 45h, 46h, 47h, 48h, 48h 30min, 49h, 50h and 52h after administration of study drug. During the dialysis (i.e. from 44h 15min to 48h post-dose), the blood samples were taken from both the inflow and outflow of the dialyser. Seven dialysate fluid samples of 25 ml were collected prior and at 15min, 30min, 1h, 2h, 3h and 4h after the start of the dialysis.

#### **Analytical method**

Levocetirizine (ucb 28556) and ucb P026 concentrations were determined in 125 plasma

samples and 35 dialysate samples using a validated LC/MS method. Response increased linearly for both matrices with concentration in the 2-500 ng/mL range for levocetirizine and in the 2-250 ng/mL range for ucb P026.

During the validation in plasma, at the lower limit of quantification (2 ng/mL), the between run imprecision (CV%) was less than 10% and accuracy was better than 89% for both compounds.

The imprecision (CV%) and the inaccuracy (% deviation) of quality control samples in plasma and dialysate were tabulated below (Table 22) at all levels and for both analytes. For both matrices and for both analytes, these results meet the regulatory criterion [refer to the guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy.

**Table 22.** Summary data for precision (%CV) and accuracy (% deviation) of quality control samples during sample analyses

	Quality Control Samples		
<b>ucb 28856 Plasma</b>	<b>4 ng/mL</b>	<b>40 ng/mL</b>	<b>400 ng/mL</b>
Precision (%CV)	10.0	10.2	6.8
Accuracy(% deviation)	+14.0	+4.7	+2.2
<b>P026 Plasma</b>	<b>3 ng/mL</b>	<b>30 ng/mL</b>	<b>225 ng/mL</b>
Precision (%CV)	12.1	10.7	5.4
Accuracy(% deviation)	+1.6	+3.8	-1.7
<b>ucb 28556 Dialysate</b>	<b>4 ng/mL</b>	<b>40 ng/mL</b>	<b>400 ng/mL</b>
Precision (%CV)	7.9	4.6	3.8
Accuracy(% deviation)	+3.6	+4.8	+0.05
<b>P026 Dialysate</b>	<b>3 ng/mL</b>	<b>30 ng/mL</b>	<b>225 ng/mL</b>
Precision (%CV)	2.2	5.7	3.4
Accuracy(% deviation)	+16.7	+12.0	+11.7

## RESULTS

In ESRD subjects, the mean (SD) plasma concentration of levocetirizine was maximal ( $355 \pm 96$  ng/ml) at 30 min, the first post-dose sampling time point. Concentrations then declined slowly to 98.7 (22.0) ng/ml at 44 hours post-dose, just before starting the dialysis session. Mean (SD) plasma levocetirizine concentration-time profile is captured in Figure 10.

During the 4-hour dialysis session, levocetirizine decreased by 21% in the systemic circulation. After the termination of dialysis, there was no rebound in plasma concentrations. At the last sampling time (52 h), the average (SD) plasma concentration was 65.2 (21.7) ng/ml, i.e. still sufficiently measurable in all subjects.

In the course of dialysis, the mean ratio of outflow to inflow concentrations in the dialyser was 0.88, which remained stable during the dialysis session.

Levocetirizine PK parameters were derived from plasma concentrations available up to 44 hours post-dose before the start of the dialysis session. This limited the evaluation of elimination PK parameters such as  $AUC_{0-\infty}$  and  $t_{1/2}$ . The mean extrapolated part of AUC was 46%, too large to reliably calculate  $\lambda_z$ . Nevertheless, an approximate value of  $t_{1/2}$  was reported to be about 41 h; about 4-fold that of healthy subjects. The mean total body clearance (CL/F) was reduced by about 80% when compared to healthy subjects (35.5 vs. 7.2 mL/min). The mean (SD) peak concentration of 358.0 (90.6) ng/mL, about 62% greater than in healthy subjects, was achieved after 30 minutes of dosing. The approximated value of mean AUC in ESRD patients (12579 ng.h/mL) was found to be considerably greater than that in subjects (2213 ng.hr/mL) with normal renal function.

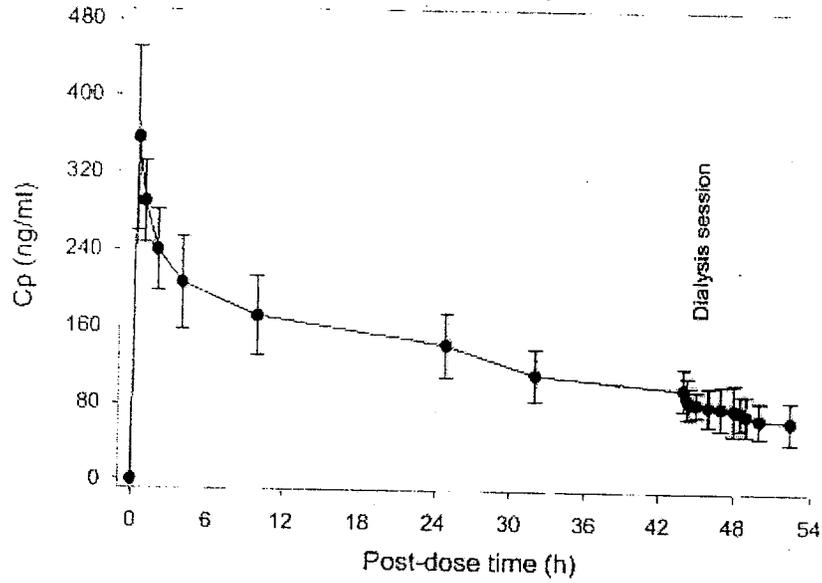
The plasma protein binding of levocetirizine as determined by equilibrium dialysis was 86.6, generally similar to that shown in healthy subjects. The mean (SD) apparent total body clearance of unbound levocetirizine was calculated to be 54.7 (22.0) ml/min, i.e. about 6.7-fold lower than in healthy subjects [360.1 (67.3) ml/min].

The average (SD) levocetirizine hemodialysis clearance was 22.2 (5.5) mL/min and was about three times higher than the apparent total body clearance observed outside the dialysis session. The total amount of drug removed during a standard 4-hour hemodialysis procedure was <8.7% with a large inter-individual variability (SD = 22%, range = -23.3 to 25.5%). The amount (mean  $\pm$  SD) of drug remaining in the body after the hemodialysis was 1.95  $\pm$  0.88 mg. Very low (<6ng/ml) concentrations of levocetirizine were found in the dialysate fluid. The amount of ucb P026 removed from the systemic circulation was equivalent to 0.8% (0.4% - 1.1%) of the administered dose of levocetirizine. However, no quantifiable P026 concentrations were found in the dialysate fluid as they are all BLOQ.

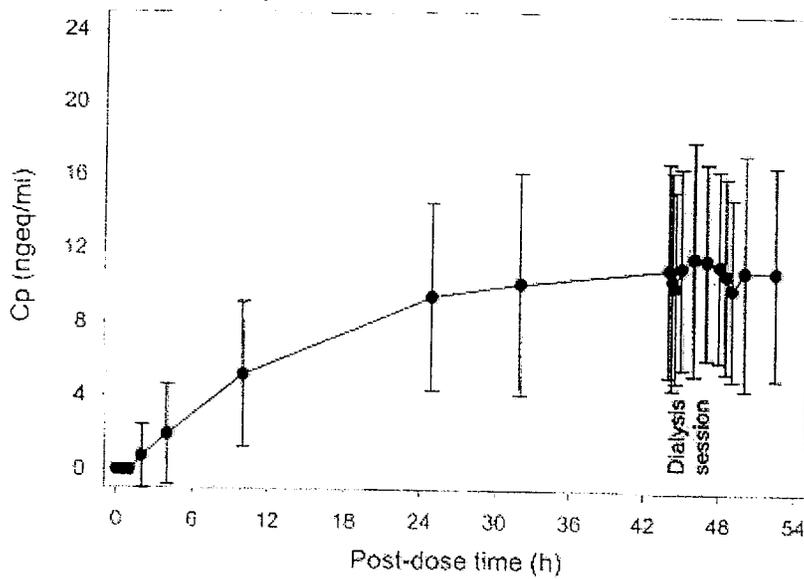
Mean (SD) plasma P026 concentration-time profile in ESRD patients is presented in Figure 11. In ESRD patients, plasma concentrations of ucb 28856 were measurable in all subjects from 24h post-dose onwards. Peak plasma concentration of 11.1 (5.8) was achieved at 44h post-dose and essentially remained unchanged during dialysis. In the course of dialysis, the mean ratio of outflow to inflow concentrations in the dialyser was 0.91, which remained stable during the dialysis session. The mean (SD)  $AUC_{0-44h}$  of P026 was estimated to be 333 (205) ng.hr/mL (Table 23), which was about 5.1% of the parent drug exposure in the same time period, comparing well with the same ratio calculated in healthy subjects (7.7%).

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**Figure 10.** Mean (SD) levocetirizine plasma concentration-time profile after single-dose oral administration of 5 mg ucb 28856 in subjects with ESRD undergoing hemodialysis.



**Figure 11.** Mean (SD) P026 (levocetirizine metabolite) plasma concentration-time profile after single-dose oral administration of 5 mg ucb 28856 in subjects with ESRD undergoing hemodialysis.



**Table 23.** Plasma PK parameters of levocetirizine (total and unbound) and P026 following single-dose oral administration of 5 mg ucb 28856 in subjects with end-stage renal disease (ESRD)

	ucb 28556		ucb P026
	total	unbound	
C <sub>max</sub> (ng/ml)	358 (243 - 434)	47.3 (30.1 - 61.2)	-
t <sub>max</sub> (h)	0.50 (0.50 - 1.07)		-
AUC <sub>0-48h</sub> (ng.h/ml)	6575 (4776 - 8262)	870 (592 - 1013)	333 (131 - 634)
AUC (ng.h/ml)	12579 (7264 - 17040)	1681 (901 - 2303)	-
V <sub>area</sub> /F (l)	23.7 (17.1 - 32.6)	177 (139 - 210)	-
V <sub>area</sub> /F (l/kg)	0.39 (0.31 - 0.52)	2.91 (2.35 - 3.62)	-
CL/F (ml/min)	7.17 (4.89 - 11.5)	54.7 (36.2 - 92.5)	-
CL/F (ml/min/kg)	0.12 (0.07 - 0.20)	0.93 (0.57 - 1.60)	-
t <sub>1/2</sub> (h)	41.0 (26.2 - 60.9)		-

(t<sub>max</sub> value is median (range), other values are means (range), see section 14.2.

## REVIEWER'S COMMENTS AND CONCLUSIONS

Consistent with the results obtained from study A230, this study further confirmed that levocetirizine is primarily eliminated by urinary excretion. Systemic exposure of levocetirizine (AUC) increased by 5.7-fold in ESRD patients compared to subjects with normal renal function. This study shows that the hemodialysis has a minor effect on the removal of levocetirizine. Three subjects (out of 5) reported somnolence, which is highly likely to be study drug related. The drug is proposed to be contraindicated in ESRD patients and in patients undergoing hemodialysis.

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## Study A184

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### **DOUBLE-BLIND CROSSOVER COMPARISON AT RANDOM BETWEEN CETIRIZINE (5 MG, SINGLE ORAL INTAKE), UCB 28556 (2.5 MG, SINGLE ORAL INTAKE) AND UCB 28557 (2.5 MG, SINGLE ORAL INTAKE) ON THE HISTAMINE-INDUCED WHEAL AND FLARE SKIN REACTION IN NORMAL HEALTHY VOLUNTEERS**

**Protocol No:** RPCE92A0901  
**Date of Final Report:** November 13, 1993  
**Phase:** I

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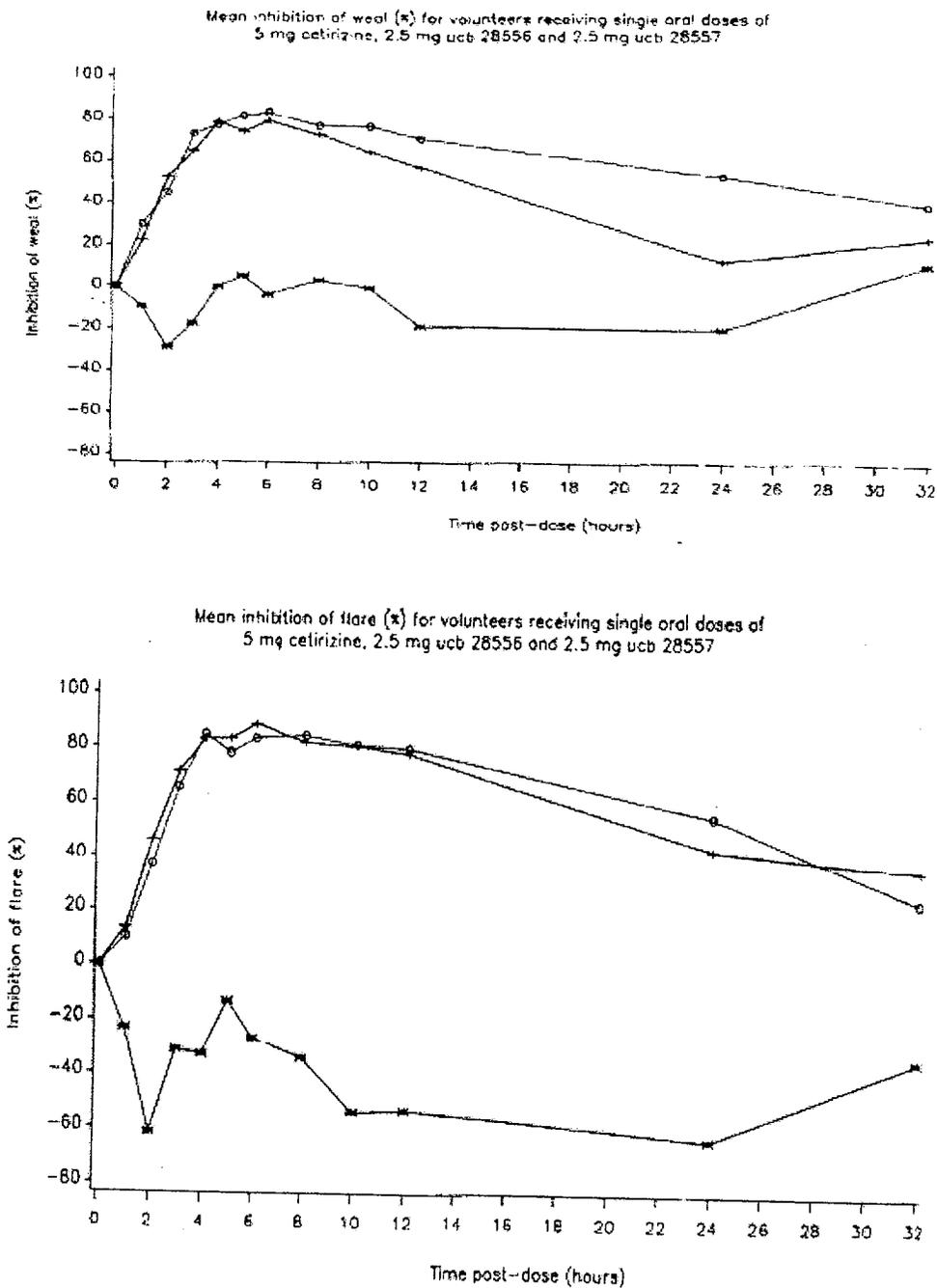
This was a double-blind, balanced, three-way crossover study in three cohorts of 18 healthy male volunteers to compare the effect of 5 mg cetirizine and its two enantiomers, 2.5 mg levocetirizine (ucb28556) and 2.5 mg dextrocetirizine (ucb28557) on the histamine-induced weal and flare skin reaction. Eighteen healthy subjects completed the study. The objective of this pharmacodynamic study was to assess and compare the antihistaminic activities of these three compounds.

The single-dose of the test articles were administered orally with a 7 day washout between the treatments. Histamine-induced weal and flare responses were induced by skin prick-test with histamine concentration (100 mg/mL) and were recorded before dosing and at 1, 2, 3, 4, 5, 6, 8, 12, 24 and 32 h after dosing. Blood samples for the determination of plasma concentration of cetirizine and the two enantiomers were taken before dosing and at 4 and 8 h after dosing. Urine samples for the determination of urinary concentrations of cetirizine and its two enantiomers were taken at -1 to 0 h (pre-dose) and at 0-4, 4-8, 8-12, 12-24 and 24-32 h post-dose.

Oral administration of levocetirizine and cetirizine caused a marked inhibition of histamine-induced weal and flare from the first assessment at 1 h post-dose to the last assessment at 32 h post-dose. The inhibition profiles of levocetirizine and cetirizine were approximately similar with maximum inhibition occurring at approximately 6 h post-dose (Figure 12).

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**Figure 12.** Time-course of mean inhibition of wheal and flare following administration of cetirizine (x), levocetirizine (o), and dextrocetirizine (\*)



Cetirizine and levocetirizine exhibited mean inhibition of wheal values of 88% and 92% and flare values of 94% and 95%, respectively (Table 24). Levocetirizine was found to be significantly more active than cetirizine, however the mean values were similar for both

compounds. The mean  $AUC_{inh(0-32h)}$  weal values were 1314 and 1938%.hr for cetirizine and levocetirizine, respectively. The corresponding  $AUC_{inh(0-32h)}$  flare values were 1877 and 1946%.hr, respectively. In contrast, dextrolevocetirizine exhibited no clear change in the inhibition of wheal and flare reaction.

**Table 24.** Comparison between Levocetirizine (2.5 mg) and Cetirizine (5 mg) on the Wheal and Flare Parameters

Measure	Parameter	Mean levocetirizine	Mean cetirizine	Ratio	p-value	90% confidence interval of ratio	
Wheal area	$AUC_{inh(0-32h)}$ (%.h)	1938	1314	1.47	0.018	1.16	1.79
	$AUC_{(0-32h)}$ (mm <sup>2</sup> .h)	742	820	0.91	0.22	0.79	1.04
	$A_{max}^*$ (%)	92.1	88.3	1.04	0.056	1.01	1.08
Flare area	$AUC_{inh(0-32h)}$ (%.h)	1946	1877	1.04	0.74	0.85	1.22
	$AUC_{(0-32h)}$ (mm <sup>2</sup> .h)	10413	10919	0.95	0.75	0.74	1.23
	$I_{max}^*$ (%)	95.2	94.3	1.01	0.42	0.99	1.03

\* Ratio of geometric means and corresponding 90% confidence interval.

Maximum urinary excretion of cetirizine and both enantiomers occurred during the 0 to 4 hr collection period with mean values of 17.6, 16.3 and 17.2% of dose excreted for cetirizine, levocetirizine and dextrocetirizine respectively. Mean cumulative excretion showed a progressive increase to 55.2, 57.8 and 50.4% of dose at 32 h post-dose for cetirizine, levocetirizine and dextrocetirizine, respectively. Chiral analysis of the excretion of levocetirizine and dextrocetirizine following the administration of cetirizine also showed maximum urinary excretion during the 0 to 4 h period with a steady increase in mean cumulative excretion to 60.8 and 50.9% of dose by 32 h post-dose. However, in both the achiral and chiral analyses the cumulative excretion of levocetirizine was greater than dextrocetirizine. Plasma exposure data further confirmed this observation where mean plasma concentrations at 4 h post dose were 128, 78 and 41 ng/mL for cetirizine (5 mg), levocetirizine (2.5 mg) and dextrocetirizine (2.5 mg) respectively.

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### 4.3. Consult Review

*Pharmacometric Review (TQT study A00419 review submitted in DFS on March 7, 2007)*

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#### 4.4. OCP Filing/Review Form

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
General Information About the Submission				
Information		Information		
NDA Number	22-064	Brand Name	Xyzal	
OCP Division	DCP2	Generic Name	Levocetirizine dihydrochloride	
Medical Division	DPADP	Drug Class	Oral H1-histamine receptor antagonist	
OCP Reviewer	Partha Roy	Indication(s)	Symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), & chronic idiopathic urticaria (CIU) in adults and children ≥ 6 yrs	
OCP Team Leader	Emmanuel Fadiran	Dosage Form	Oral tablet	
Date of Submission	25 July 2006	Dosing Regimen	5 mg	
Estimated Due Date of OCP Review	25 Feb 2007	Route of Administration	Oral	
PDUFA Due Date	25 May 2007	Sponsor	UCB Inc.	
Division Due Date	25 Mar 2007	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	X			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:	X	X	X	
Isozyme characterization:	X	X	X	
Blood/plasma ratio:	X	X	X	
Plasma protein binding:	X	X	X	
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:	X	X	X	
multiple dose:	x	x	x	
<i>Patients-</i>				
single dose:	X	X	X	
multiple dose:	x	x	x	
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	X	X	
fasting / non-fasting multiple dose:	x	x	x	
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	x	x	x	
<b>Subpopulation studies -</b>				
ethnicity:				
gender:	x	x	x	
pediatrics:	x	x	x	
geriatrics:				
renal impairment:	x	x	x	
hepatic impairment:				

PD:				
Phase 2:	X	X	X	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	x	x	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	x	x	x	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	x	x	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	X	X	
Dissolution:	X	X	X	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	x	x	
Total Number of Studies	25	14	8	Full study reports for 14 studies submitted out of which 8 studies reviewed in detail. Study synopses for the rest of the studies were also submitted.
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> <li>1. Demonstration of PK equivalence and PD comparability between levocetirizine 2.5 and 5 mg AND cetirizine 5 and 10 mg.</li> <li>2. PK in children 6-11 years compared to adults</li> <li>3. ECG and PK data from a thorough QT/QTc study</li> </ol>		
Other comments or information not included above				
Primary reviewer Signature and Date	Partha Roy 20 September 2006			
Secondary reviewer Signature and Date				

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

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Partha Roy  
3/27/2007 09:59:49 AM  
PHARMACOLOGIST/TOXICOLOGIST

Please review the draft labeling comments

Emmanuel Fadiran  
3/27/2007 12:13:00 PM  
BIOPHARMACEUTICS  
I concur.