CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-565

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-565	Submission Date(s): 12/19/02
Brand Name	RELESTAT
Generic Name	Epinastine HCl
Reviewer	E. Dennis Bashaw, Pharm.D.
Dep. Director (secondary review)	Arzu Selen, Ph.D.
OCPB Division	DPE-III
ORM division	HFD-550
Sponsor	Allergan
Relevant IND(s)	61,025
Submission Type; Code	1-S
Formulation; Strength(s)	0.05% Ophthalmic Soln.
Indication	Prevention of the signs and symptoms of Allergic Conjunctivitis

1 Executive Summary

Allergic conjunctivitis is one of the most common eye disorders, affecting an estimated 20% of the general population. The action of histamine at the H_1 receptor site mediates most of the symptoms of allergic conjunctivitis. While itching is exclusively mediated through the H_1 receptor, symptoms such as hyperemia, lid swelling, and chemosis are also mediated through the H_2 receptor.

Epinastine is a nonsedating antihistamine with mast cell stabilizing properties. According to the sponsor, nonclinical studies have shown epinastine to be a highly effective H_1-receptor antagonist with potent antihistamine activity; marked affinity for α–1, α–2, and 5-HT_2 receptors; and low affinity for histamine H_2 receptors, muscarinic receptors, and β-receptors. Epinastine has also been shown to inhibit the release of many chemical mediators and is therefore considered to have mast cell stabilizing activity.

This NDA is only for the 0.05% ophthalmic solution formulation of epinastine HCl for the prevention of [redacted] allergic conjunctivitis. The same product was approved in Sweden on 18 October 2002 under the trade name RELESTAT. Epinastine HCl is also available as a 10 and 20mg tablet and as a 200mg/ml syrup in over 15 Asian and European countries under the tradenames: ALESION, FLURINOL, EPINAS, and TALERC.

In this NDA the sponsor has submitted the results from 10 in vivo pharmacokinetic studies with various formulations of epinastine. Of these studies, only one investigated

the systemic availability of epinastine opth. Soln. in patients with allergic conjunctivitis. The rest of the studies used either the oral or a non-approved IV formulation.

1.1 Recommendation

The sponsor has adequately addressed the Clinical Pharmacology/Biopharmaceutic requirements of 21CFR320 for epinastine HCl 0.05% ophthalmic solution.

1.2 Phase IV Commitments

There are no outstanding phase IV commitments from a Clinical Pharmacology/ Biopharmaceutic Perspective.

E. Dennis Bashaw, Pharm.D.
Team Leader, HFD-540/550/560

Secondary Review: Arzu Selen, Ph.D., Deputy Director, DPE-III_____

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3 Summary of CPB Findings

The ocular pharmacokinetics of epinastine following single- and multiple-dose administration of a 0.05% ophthalmic solution were studied in 14 patients with allergic conjunctivitis. Systemic epinastine exposure was low following ophthalmic dosing. The maximum plasma concentration (Cmax) in patients was 0.025 ± 0.008 ng/mL (Tmax 4.46 ± 2.87 hr) following a single dose and 0.042 ± 0.014 ng/mL (Tmax 1.81 ± 0.93 hr) following twice-daily dosing. The pharmacokinetics of topical epinastine were linear, with single-dose AUC predictive of the multiple-dose AUC value. Terminal plasma

elimination half-life after single-dose (9.26 ± 4.28 hr) and twice-daily dosing (11.9 ± 11.6 hr) was similar to that observed after oral and intravenous administration.

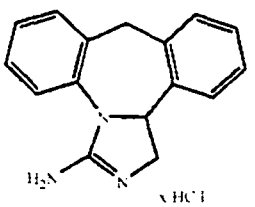
Tear epinastine concentrations peaked rapidly, and local drug concentration was substantial (Cmax 27.1 ± 46.2 µg/mL Tmax 0.033 ±0.043 hr). Subsequently, drug concentrations in tear declined rapidly until 30 minutes after dosing, beyond which a slower exponential phase was apparent. Epinastine HCl 0.05% ophthalmic solution was safe and well tolerated after single and multiple ophthalmic doses. Following ophthalmic dosing with epinastine HCl, the plasma concentrations in humans are much less than the exposure following oral dosing. Following a single dose of epinastine HCl 0.05% ophthalmic solution in patients with allergic conjunctivitis, the Cmax and AUC value is approximately 600 and 300 times less than the Cmax and AUC following a single 20 mg oral dose in humans (Cmax [redacted] ng/mL and AUC 143 – 468 ng·hr/mL).

4 QBR

4.1 General Attributes

What is epinastine and how is it formulated?

The product proposed in this New Drug Application is epinastine HCl 0.05% ophthalmic solution. The ophthalmic solution was originally developed by Boehringer Ingelheim Pharma KG, Ingelheim am Rhein, Germany (BI), and subsequently licensed to Allergan.



Molecular Formula

$C_{16}H_{15}N_3 \cdot HCl$

(R,S)-3-Amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride

or

1H-Dibenz[c,f]imidazo[1,5-a]azepin-3-amine, 9,13b-dihydro-, hydrochloride

During its development epinastine HCl was also known as AGN 198927-A and WAL-801-CL.

Epinastine HCl 0.05% ophthalmic solution is a clear, colorless, isotonic solution preserved with benzalkonium chloride (BAK).

Table 6.8.1-2 Ophthalmic Drug Formulation Ingredients

Names of Ingredients	Unit or Percentage Formula (% w/v)	Function
Active substance		
Epinastine HCl	0.05	Active Ingredient
Excipients		
Benzalkonium Chloride	0.01	Preservative
[redacted]	[redacted]	[redacted]
Sodium Chloride	[redacted]	[redacted]
Disodium Edetate	[redacted]	[redacted]
Sodium Hydroxide	[redacted]	[redacted]
Sodium Hydroxide and/or Hydrochloric Acid	[redacted]	[redacted]
Purified Water	[redacted]	[redacted]

Is epinastine approved in other countries?

Yes, as noted previously, epinastine as an ophthalmic formulation is approved in Sweden under the same tradename of RELESTAT. The oral dosage forms, for systemic anti-histaminic activity, are approved in Europe and in Asia in a number (>15) of countries.

4.2 General Clinical Pharmacology

How does epinastine compare to other antihistaminic agents?

(this information was developed both from the NDA and the pharmacology review)
In in vitro models of antihistaminic activity, epinastine displays a high binding affinity for the H_1-receptor and 400 times lower affinity for the histamine H_2-receptor. The H_1-receptor binding affinity for epinastine was higher (IC_{50} = 9.8 nM) compared to other potent antihistamines: terfenadine (77 nM) and astemizole (15 nM). The potent antihistaminic H_1-receptor activity was confirmed in functional assays using histamine-induced contractions in isolated guinea pig ileum (its potency exceeded that of terfenadine and astemizole by the factors 142 and 38), lung and rectum preparations. Its high H_1-receptor subtype selectivity was confirmed in functional assays using isolated guinea pig atrium in which, with up to 10-μM of epinastine, no histamine H_2 antagonistic effect was detectable. No differences were found between binding to central and peripheral H_1-receptor.

Is epinastine a sedating antihistamine?

Besides its high affinity for the H_1-receptor, epinastine possesses considerable affinity for the α_{-1}, α_{-2}, and the 5-HT_2–receptor. Animal studies demonstrating the alpha-adrenergic-blocking potency of epinastine found that it was in the same range as that of phentolamine, raising the issue of sedative effects in vivo. However, animal studies have also demonstrated that epinastine does not penetrate the blood/brain barrier and thus is devoid of central effects. This coupled with a low binding affinity for cholinergic, dopaminergic and a variety of other receptor sites suggests that epinastine would have a favorable side effect profile.

How was the dose selected?

Topical ocular antihistamines are evaluated using the conjunctival antigen challenge (CAC) it involves instillation into the inferior conjunctival fornix of a specified dilution of a standard antigen preparation to which the patient is sensitive. This evokes immediate clinical symptoms and signs of acute allergic conjunctivitis. The model can be further refined by titrating increasing concentrations of a specific allergen until a clinically significant and observable change in symptoms is evoked. The test can be used to judge the efficacy and/or duration of action of a pre-instilled treatment. For epinastine concentrations of epinastine of 0.5, 0.3, 0.1, and 0.05% were evaluated using this provocative test with instillation occuring at 15min prior to challenge. In the clinical trials all doses were found to be effective. However, a comparison of the results across studies suggested that the ocular tolerability of epinastine is dose dependent and is better for 0.05% than for 0.3%. It was these types of data that were the basis for selecting the 0.05% concentration of epinastine HCl for marketing.

4.3 Intrinsic Factors

What is the route of elimination for epinastine?

Following a single 20.6 mg oral and 5 mg intravenous dose in healthy subjects, the composition of radiolabelled material recovered in urine and feces was dependent on the route of administration. Up to 24.7% (oral) and 65.1% (intravenous) of drug related radioactivity was recovered in urine. Fecal excretion of [14C]-labeled material counted for 72.5% (oral) and 33.5% (intravenous) of the dose. Excretion of unchanged drug in urine was 21.0% (oral) and 54.0-57.5% (intravenous) of the administered dose.

Is epinastine metabolized via P-450?

Epinastine does not undergo appreciable metabolic biotransformation in man. The total proportion of metabolites in urine and feces was less than 10% following oral or intravenous dosing in man.

When incubating epinastine with microsomes expressing recombinant cytochrome P450 (CYP) isoforms, CYP3A4, 2D6, and (to a minor extent) 2B6 were found to be responsible for epinastine metabolism. In the human liver microsomes, 1-OH-epinastine (M-1) was postulated to be formed.

What is the role of the kidney in epinastine elimination?

After intravenous or oral administration, total systemic and renal clearance was approximately 50.5-55.7 and 30.5-32.4 L/hr, respectively, indicating renal excretion is the major route of elimination in man. Since renal clearance is greater than the glomerular filtration rate, an active secretory process is thought to be present in the renal tubules.

Has the pharmacokinetics of epinastine been evaluated in the presence or renal or hepatic insufficiency?

No, given the dosing paradigm, one drop in each eye twice daily, it is highly unlikely that either renal or hepatic insufficiency will cause the accumulation of excessive levels of epinastine given that much larger oral doses have been approved elsewhere.

4.4 Extrinsic Factors

What extrinsic factors have been evaluated?
In support of this NDA the effect of allergic conjunctivitis on the absorption of epinastine HCl from an ocular dosage form has been evaluated, the results of it are summarized below in the General Biopharmaceutics sub-section.

Have drug-drug interactions been evaluated?
No, the primary drugs used for the treatment of allergic conjunctivitis are antihistamine/ mast cell stabilizers, such as epinastine, lubricants (white petrolatum and mineral oil), and artificial tear solutions (normal saline). Given the low doses and low affinity for P-450, it is unlikely, at these doses to be a participant in drug-durg interactions.

What is the proposed dose of epinastine?
Epinastine is to be dosed as 1 drop in each eye, twice daily. As the proposed strength is 0.05% or 0.5mg/ml and assuming 25 drops per ml, this would work out to a total daily dose (both eyes) of 0.5mg/ml *1ml/25drops *4 drops/day= 0.08mg/day.

4.5 General Biopharmaceutics

Radiolabelled Relative Bioavailability Study (U90-206, Appendix 6.3)

In humans, the absorption of epinastine following oral administration was rapid. Following single dose administration of a [14C]-epinastine aqueous oral solution (20.6 mg) to six male volunteers, the Cmax of unchanged epinastine and [14C]-epinastine was 15.5 ng/mL and 19.9 ng-eq/mL respectively. Tmax occurred at 1.70 hours and 1.80 hours after dosing, for epinastine and total radioactivity, respectively.

The steady-state volume of distribution of epinastine was 417 L, which exceeds the volume of total body water, suggesting that epinastine distributes extensively to body tissues. Epinastine demonstrates moderate binding to plasma proteins (approximately 64.2%) at a concentration of 20 ng/mL and thus is unlikely to participate in displacement type drug interactions. In erythrocytes, the concentration of [14C]-epinastine was higher than in plasma by a factor of 1.70-2.70

Epinastine Absorption in Patients with Allergic Conjunctivitis (198027-004, Appendix 6.2)
The ocular pharmacokinetics of epinastine following single- and multiple-dose administration of a 0.05% ophthalmic solution were studied in 14 patients with allergic conjunctivitis. Systemic epinastine exposure was low following ophthalmic dosing. The maximum plasma concentration (Cmax) in patients was 0.025 ± 0.008 ng/mL (Tmax 4.46 ± 2.87 hr) following a single dose and 0.042 ± 0.014 ng/mL (Tmax 1.81 ± 0.93 hr) following twice-daily dosing. The pharmacokinetics of topical epinastine were linear, with single-dose AUC predictive of the multiple-dose AUC value. Terminal plasma elimination half-life after single-dose (9.26 ± 4.28 hr) and twice-daily dosing (11.9 ± 11.6 hr) was similar to that observed after oral and intravenous administration.

Summary PK Data

	AUC0-inf (ng*hr/ml)	AUC0-last (ng*hr/ml)	Tmax (hr)	Cmax (ng/ml)	Half-life (hr)
Day 1	0.465+/-0.216	0.172+/-0.146	4.46+/-2.87	0.025+/-0.008	9.26+/-4.28
Day 7	0.347+/-0.119	n.a.	1.81+/-0.93	0.042+/-0.014	11.90+/-11.55

The results clearly indicate that epinastine does become "bioavailable" following ophthalmic dosing in man. Plasma levels are, however, very low and are unlikely to be of systemic pharmacologic significance. Following a single dose of epinastine HCl 0.05% ophthalmic solution in patients with allergic conjunctivitis, the Cmax and AUC value is approximately 600 and 300 times less than the Cmax and AUC following a single-20 mg oral dose in humans (range: Cmax [redacted] ng/mL and AUC 143 – 468 ng·hr/mL).

In contrast to the plasma data, tear epinastine concentrations peaked rapidly, and local drug concentration was substantial (Cmax 27.1 ± 46.2 µg/mL Tmax 0.033 ±0.043 hr). Subsequently, drug concentrations in tear declined rapidly until 30 minutes after dosing, beyond which a slower exponential phase was apparent. Epinastine HCl 0.05% ophthalmic solution was safe and well tolerated after single and multiple ophthalmic doses.

4.6 Analytical

Analytical Validation for Study 198027-004

This report presents human plasma concentrations of epinastine (AGN 198027) for an ocular dose epinastine study conducted in subjects with allergic conjunctivitis under protocol #198027-004. Plasma epinastine concentrations were determined using a validated [redacted] method [redacted] with a concentration range of [redacted] ng/mL.

The [redacted] method employed [redacted] as internal standard to determine epinastine concentrations in human plasma. Briefly, the method involved [redacted]

Figure 1 Representative calibration curve of epinastine (AGN 198027) in human plasma at concentrations from [redacted]

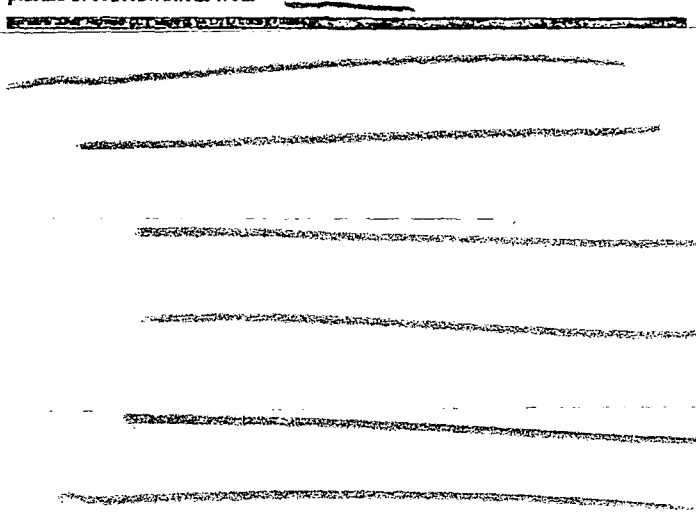


Table III: Summary of calibration curve parameters for epinastine (AGN 198027) in human plasma.

AGN 198027				
Run	**Date**	**Intercept**	**Slope**	**Correlation Coefficient (r)**
1	7/2/01	0.00583	1.72	0.999
2	7/5/01	0.00695	1.81	0.999
3	7/9/01	0.0121	1.74	0.999
4	7/18/01	0.0192	1.71	0.999
5	7/19/01	0.0136	1.72	0.998

Table IV: Summary of back-calculated concentrations of calibration standards for epinastine (AGN 198027) in human plasma.

	AGN 198027 (ng/mL)							
Mean	0.0101	0.0189	0.0307	0.0482	0.102	0.195	0.505	0.999
SD	0.0014	0.0028	0.0046	0.0042	0.007	0.011	0.023	0.019
%CV								
%Accuracy								
n								

a = outlier
b = no response

Table V: Summary of inter-day mean concentrations of epinastine (AGN 198027) measured from human plasma quality control samples.

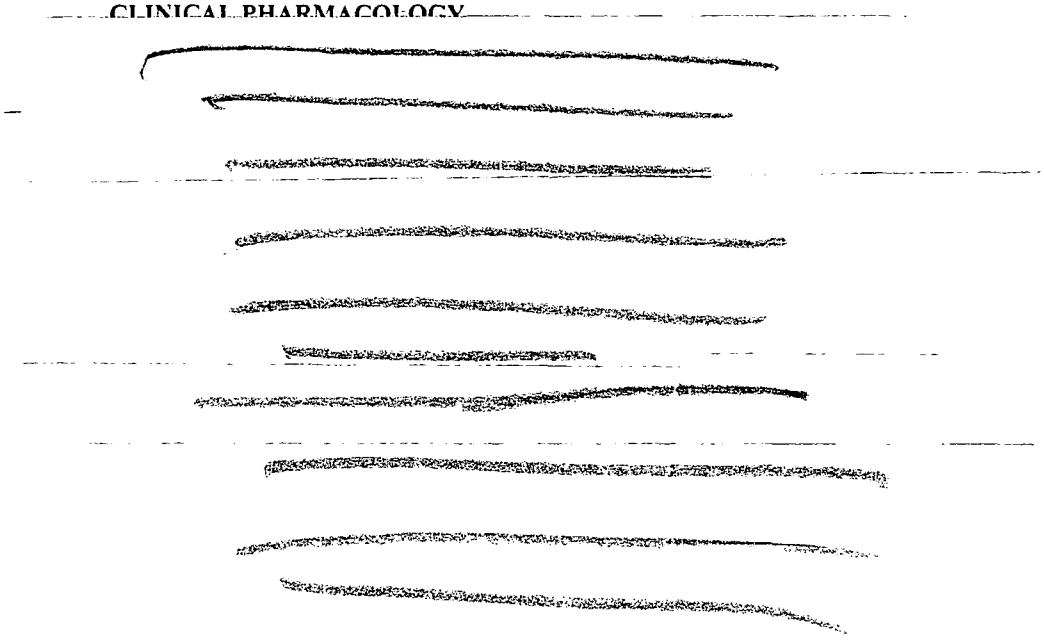
	AGN 198027 (ng/mL)		
nominal	0.02	0.1	0.5
7/2/01	0.0227	0.0960	0.394
	0.0189	0.0990	0.403
	0.0274	0.0914	0.447
7/5/01	0.0226	0.0975	0.410
	0.0184	0.0999	0.400
	0.0132	0.0934	0.351
7/9/01	0.0169	0.0939	0.358
	0.0233	0.0987	0.403
	0.0192	0.0833	0.411
7/18/01	0.0210	0.0885	0.405
	a	0.138	0.400
	0.0195	0.0992	0.354
7/19/01	0.0214	0.0911	0.412
	b	b	0.457
	0.0173	0.0944	0.400
	b	b	0.461
	0.0198	0.0958	0.403
	b	b	0.420
Mean	0.0201	0.0973	0.405
SD	0.0034	0.0121	0.031
%CV			
%Accuracy			
n			

a = no response

b = additional replicate not analyzed

5 Labeling

The full text of the proposed package insert is attached as item 6.1 in the appendix The clinical pharmacology section in its entirety is reproduced below.



The first two paragraphs of the Clinical Pharmacology section are referred to the reviewing pharmacologist for comment as they relate to issues under their purview. As for the third paragraph, it primarily concerns the results from trial 198027-004, the following underlined revisions are recommended to provide additional study details.

These revisions should be forwarded to the sponsor.

Appendix

Proposed Labeling

Detailed Report of Pivotal Study

PK-01-126: A pharmacokinetic report of epinastine AGN 198027 for study 198027-004

Supportive Studies

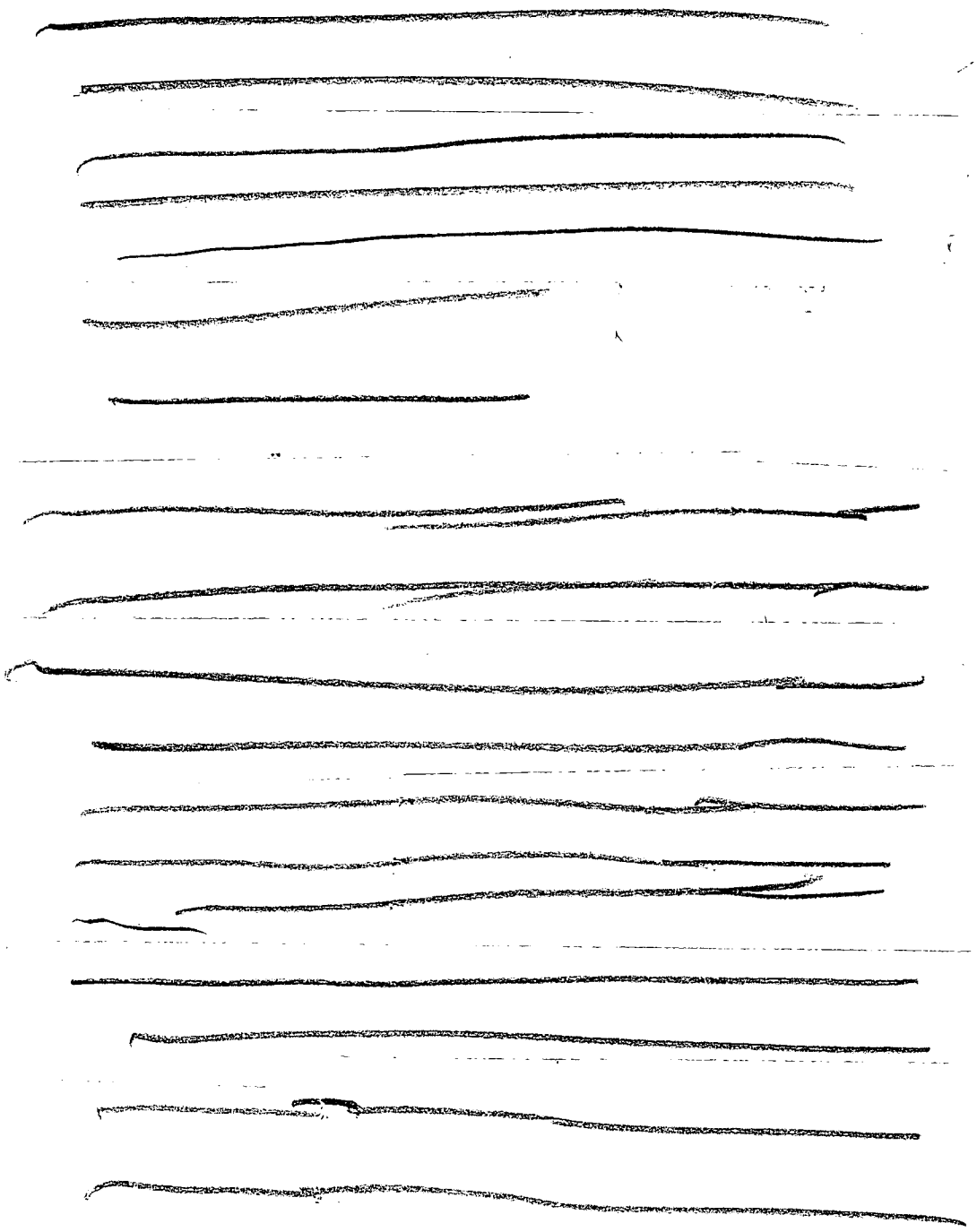
-U90-0206: Investigation of pharmacokinetics and metabolism of WAL 801 CL in man after administration of single radioactive doses

-Kishimoto 1998: Metabolism of epinastine, a histamine H1 receptor antagonist, in humans

6 Appendix

6.1 proposed labeling

SPONSOR'S PROPOSED PACKAGE INSERT



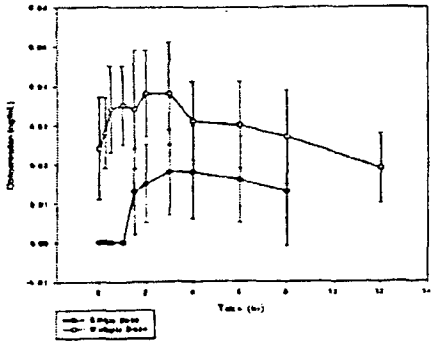
3 Draft Labeling Page(s) Withheld

6.2 Individual Study Reviews-Pivotal

A Single-Center, Open-Label Study of the Plasma and Tear Pharmacokinetics and Safety Following Topical Administration of Epinastine HCl 0.05% Ophthalmic Solution as a Single Dose Followed by Twice and Three Times Daily Dosing to Patients with Allergic Conjunctivitis (Report PK-01-126/Study 198027-004)

This was an open-label pharmacokinetics study. One drop (approximately 30 microliters in each eye) of epinastine HCl 0.05% ophthalmic solution was administered to 14 patients with allergic conjunctivitis on Day 0. This was followed by twice daily (every 12 hours) dosing for 5-1/2 days from Day 1 to the morning on Day 6. On Day 7, one drop of epinastine HCl 0.05% ophthalmic solution was administered every four hours to both eyes of each patient for three doses. All dosing was done by study personnel Blood samples were taken at specified times on Days 0, 1, and 4 through 7 to characterize the systemic pharmacokinetics of topically administered epinastine. Tear samples were collected on Day 7 to assess local drug concentrations in the eyes. Plasma and tear epinastine concentrations were determined using a validated [redacted] method with lower limits of quantitation (LLOQ) of [redacted] ng/mL and [redacted], for plasma and tear, respectively, see analytical validation. Plasma pharmacokinetic parameters were calculated using non-compartmental techniques.

FIGURE 1: MEAN (SD) EPINASTINE PLASMA CONCENTRATION TIME PROFILES FOLLOWING A SINGLE AND TWICE DAILY OCULAR APPLICATIONS OF EPINASTINE HCL 0.05 % SOLUTION FOR 5-1/2 DAYS TO PATIENTS WITH ALLERGIC CONJUNCTIVITIS



Examination of the resulting plasma level profiles shows that the plasma levels are for the most part either at or just above the limit of detection following a single dose. Following

steady-state dosing the levels are somewhat higher but still highly variable. Reproduced in the following tables are the indivdiual and mean parameter values from this study.

Table 4. INDIVIDUAL AND MEAN (SD, CV,%) PLASMA EPINASTINE PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE DOSE ADMINISTRATION OF EPINASTINE HCL 0.05% SOLUTION IN 14 PATIENTS WITH ALLERGIC CONJUNCTIVITIS

Day	Patient	$AUC_{0-\infty}$ (ng • hr/mL)	AUC_{0-last} (ng • hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	Half-life (hr)
0	1001	0.727	0.447	4.00		14.29
	1002	NC	0.140	12.00		NC
	1003	NC	0.183	3.00		NC
	1004	0.438	0.196	2.00		7.91
	1005	0.196	0.099	4.00		5.61
	1006	0.256	0.150	0.50		3.97
	1007	NC	0.021	3.00		NC
	1008	NC	0.081	4.00		NC
	1009	0.485	0.302	6.00		11.35
	1010	NC	0.003	2.00		NC
	1011	0.763	0.455	8.00		14.83
	1012	0.389	0.238	4.00		6.83
	1013	NC	0.078	4.00		NC
	1014	NC	0.014	6.00		NC
	N	7	14	14	14	7
	Mean	0.465	0.172	4.46	0.025	9.26
	SD	0.216	0.146	2.87	0.008	4.28
	CV%					

NC: Not calculable

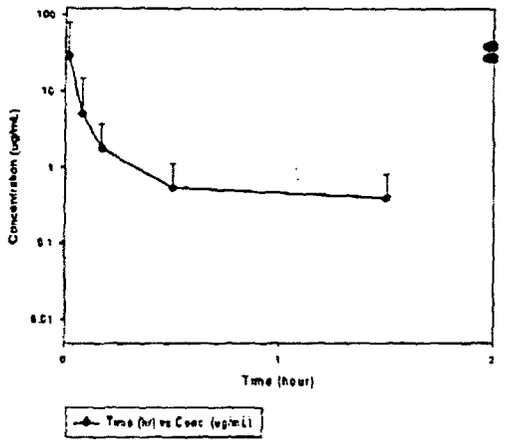
A closer examination of the individual parameter values explains one of the peculiarities of the data, namely that the AUC value for multiple dose is smaller than that following a single dose. This is due to the fact that 7 subjects in the single phase of the study had plasma levels that were either below the limit of detect or were erratic to the point that a full profile could not be determine

Table 5. INDIVIDUAL AND MEAN (SD, CV,%) PLASMA EPINASTINE PHARMACOKINETIC PARAMETERS FOLLOWING TWICE DAILY DOSE ADMINISTRATION OF EPINASTINE HCL 0.05% SOLUTION FOR 5-1/2 DAYS IN 14 PATIENTS WITH ALLERGIC CONJUNCTIVITIS

Day	Patient	AUC_{0-12} (ng • hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	Half-life (hr)
6	1001	0.368	2.00		14.92
	1002	0.244	1.00		7.66
	1003	0.575	1.50		7.62
	1004	0.418	2.00		8.67
	1005	0.217	3.00		17.11
	1006	0.339	2.00		4.78
	1007	0.254	3.00		5.30
	1008	0.406	0.00		10.28
	1009	0.482	3.00		9.31
	1010	0.188	2.00		6.38
	1011	0.482	1.50		6.08
	1013	0.272	2.00		6.10
	1014	0.271	0.50		48.44
	N	13	13	13	13
	Mean	0.347	1.81	0.042	11.90
	SD	0.119	0.93	0.014	11.55
	CV%				

NC: not calculable

FIGURE 2: MEAN (SD) EPINASTINE TEAR CONCENTRATION TIME PROFILES FOLLOWING A THREE TIMES DAILY OCULAR APPLICATIONS OF EPINASTINE HCL 0.05% SOLUTION TO PATIENTS WITH ALLERGIC CONJUNCTIVITIS



As for the tear data, it was collected following super-maximal dosing, i.e. dosing every 4 hours. Even so the material is rapidly cleared from the eye by ocular mechanisms (i.e. tear production, blinking, draining, etc.) such that levels approach the limit of detection by a half-hour following dosing. This data suggests that any prolonged antihistaminic activity must be due to uptake into local tissues/inflammatory cells.

Table 7. INDIVIDUAL AND MEAN (SD, CV, %) TEAR EPINASTINE PHARMACOKINETIC PARAMETERS FOLLOWING THREE TIMES DAILY DOSE ADMINISTRATION OF EPINASTINE HCL 0.05% SOLUTION IN 14 PATIENTS WITH ALLERGIC CONJUNCTIVITIS

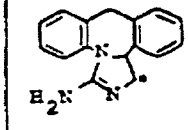
Patient	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-last}}$ (µg • hr/mL)
1001	[illegible]	0.017	12.6
1002	[illegible]	0.170	0.0609
1003	[illegible]	0.017	6.99
1004	[illegible]	0.017	1.74
1005	[illegible]	0.017	1.19
1006	[illegible]	0.083	2.69
1007	[illegible]	0.017	2.64
1008	[illegible]	0.017	0.708
1009	[illegible]	0.017	3.24
1010	[illegible]	0.017	3.93
1011	[illegible]	0.017	0.374
1012	[illegible]	0.017	0.720
1013	[illegible]	0.017	3.06
1014	[illegible]	0.017	0.423
N	14	14	14
Mean	27.1	0.033	2.89
SD	46.2	0.043	3.36
CV%			

Name of company: Boehringer Ingelheim KG	TABULATED STUDY REPORT	
Name of finished product		
Name of active ingredient: Epinastine (WAL 801 CL)	ref. to III G 110	U90-0206
	Page / Number	

PHARMACOKINETICS Pharmacokinetics after a single dose

Ref. to document : Volume: Page: to Addendum No.:
Report date: Febr 08, 1990 Number: Study period (years): 1987

Species/strain: Man (healthy volunteers)
No of animals/sex/dose: 6 / male / 20 6 mg
Administration: oral
Formulation: aqueous solution
Anal. method:



Nuclide: 14C
Spec. radioactivity: 92 5 MBq/g
Substance analysed: Drug and 14C activity
Dosage < mg >: 20 6 (≙ 1 754 MBq)

Plasma/blood:	WAL 801 CL*)	14C activity*)
C max < ng/ml >:	15 5 (/)	19 9 ( )
T max < hours >:	1 7 (0 4- 2.1)	1 8 (0 25- 2.0)
AUC (0 - 24) <ng/ml h >:	124 68(72 4-230 6)	188 48(134 68-353.82)
AUC (0 - ∞) <ng/ml h >:	140 45(77 7-254 5)	216 00(150 4 -423 0)
CL/f <ml/min kg>:	11.6 (9 2- 15.6)	8 0 (5 7 - 11.3)
T 1/2 lambda i - z : γ:	8 1 (4 5- 8 5)	7 6 (5 8 - 9 1) [t 1/2 λ]
Binding % bound	← cf iv data →	

Excretion, recovery:	WAL 801 CL	14C activity
% in urine (0 - 24 h):	17 80± 6 70	21 9 ± 7 5
% in urine (0 - 96) :	20 58± 7 72	25 4 ± 8 8
% in feces (0 - 96) :	-	70 4 ±10 8
% in carcass (excl GIT; t):	-	-
% others (0 - , resp t):	-	-
Recovery:	20 6 ± 7 7 (CV:)	95 8 ± 3 0 (CV:)
T 1/2 R lambda i - z:		
CL R:	-	-

Further parameters:
Degree of absorption (%): 40 1 (95 % confidence interval: 36 8-43 3 %)
Abs bioavailability (%): 39.8 (95 % confidence interval: 22 7-56 3 %)

Additional informations:
Description of plasma concentration time courses of active ingredient by open three-compartment model with two preceding compartments in series
Kinetic constants of disposition preset from iv experiments (variation of ± 20 % allowed)
Calculation of absorption: Ratio of renal excretions of 14C activity
" " bioavailability: Ratio of normalized AUC values of WAL 801 CL
*Strong interindividual variability; representation of data as medians and ranges!

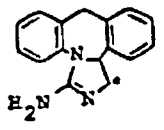
Study conducted by the applicant: yes < x > no < >
If "no", indicate the name and address of the institute that conducted the study:
Study in compliance with GLP: yes < > no < > not required < x >

Name of company Boehringer Ingelheim KG	TABULATED STUDY REPORT ref to III G 110 Page / Number	U90-0206
Name of active ingredient Epinastine (WAL 801 CL)		

PHARMACOKINETICS Pharmacokinetics after a single dose

Ref. to document.: Volume: Page: to Addendum No :
Report date: Febr 08, 1990 Number: Study period (years): 1987

Species/strain: Man (healthy volunteers)
No. of animals/sex/dose: 6 / male / 5 mg
Administration: Intravenous (short infusion over 3 min)
Formulation: Solution for iv injection
Anal. method:



x HCl

Nuclide: 14C
Spec. radioactivity: 370 MBq/g
Substance analysed: Drug and 14C activity
Dosage <mg>: 5 mg/3 min (≙ 1 715 MBq)

Plasma/blood:

C max	< ng/ml >	234.8 ± 48.7	from computer fitted curve
T max	< min >	4 1 ± 0 8	from computer fitted curve
AUC (0 - 24)	<ng/ml h>	81 6 ± 14 6	
AUC (0 - ∞)	<ng/ml h>	92 19± 16 6	
CL/f	<ml/min kg>	12 6 ± 2 6	
T 1/2 lambda i - z		α: 1 4± 0 7 min, β: 31 6 min (CV > 100 %), γ: 6 7± 2 1 [hours]	
Binding % bound		64 2±3 6 % in spiked serum at c = 20 ng/ml	

Excretion, recovery:	WAL 801 CL	14C activity
% in urine (0 - 24 h):	49 4 ± 6 8	58 2 ± 4 4
% in urine (0 - 96) :	53 5 ± 6 4	63 5 ± 3 8
% in feces (0 - 96) :	-	33 8 ± 4.9
% in carcass (excl GIT; t):	-	-
% others (0 - , resp t):	-	-
Recovery:	53.5 ± 6 4	97 3 ± 2 15 (CV:)
T 1/2 R lambda i - z:	-	-
CL R [ml/min]:	518 7 ± 83.8	384 6 ± 100 4

Further parameters:
Degree of absorption (%): -
Abs. bioavailability (%): 100

Additional informations:
Description of plasma concentration time courses of active ingredient by open three-compartment model
Trial design: Cross-over study, iv versus oral aqueous solution

Study conducted by the applicant: yes < x > no < >
If "no", indicate the name and address of the institute that conducted the study:
Study in compliance with GLP: yes < > no < > not required < x >

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As noted in the preceding study summary sheets, this was an absolute bioavailability trial undertaken by the original sponsor (Boehringer Ingelheim, KG) using a radiolabel. In this trial six men received ^{14}C labeled epinastine (20mg orally, 6mg IV). The objective of this trial was to look at drug uptake, disposition, and routes of elimination.

Fig 10 Mean plasma concentration-time curve of WAL 801 CL (ng/ml) (simulated from medians of kinetic parameters) and medians of experimental data
Mean intravenous dose 4.96 mg WAL 801 CL
Study No 640 011

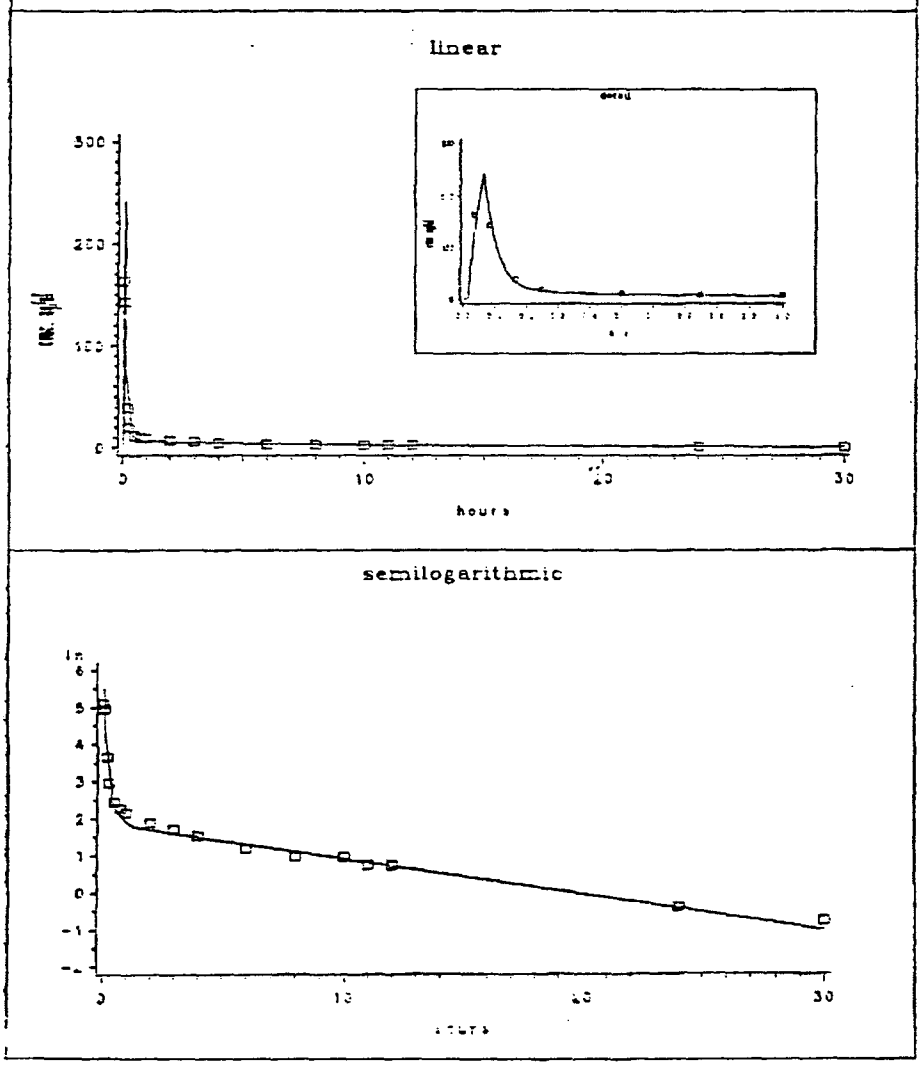


Fig 11 Mean cumulative urinary excretion of WAL 801 CL (% dose) (simulated from medians of kinetic parameters) and medians of experimental data
Mean intravenous dose 4 96 mg WAL 801 CL
Study No 640 011

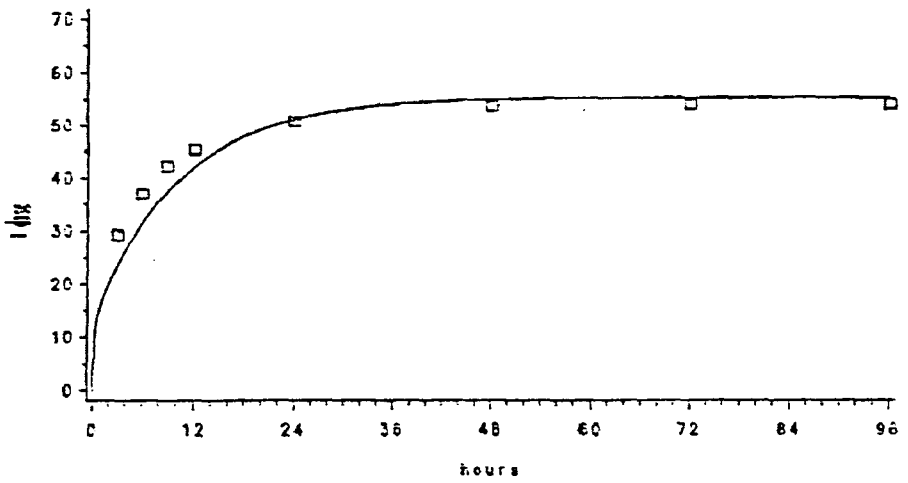
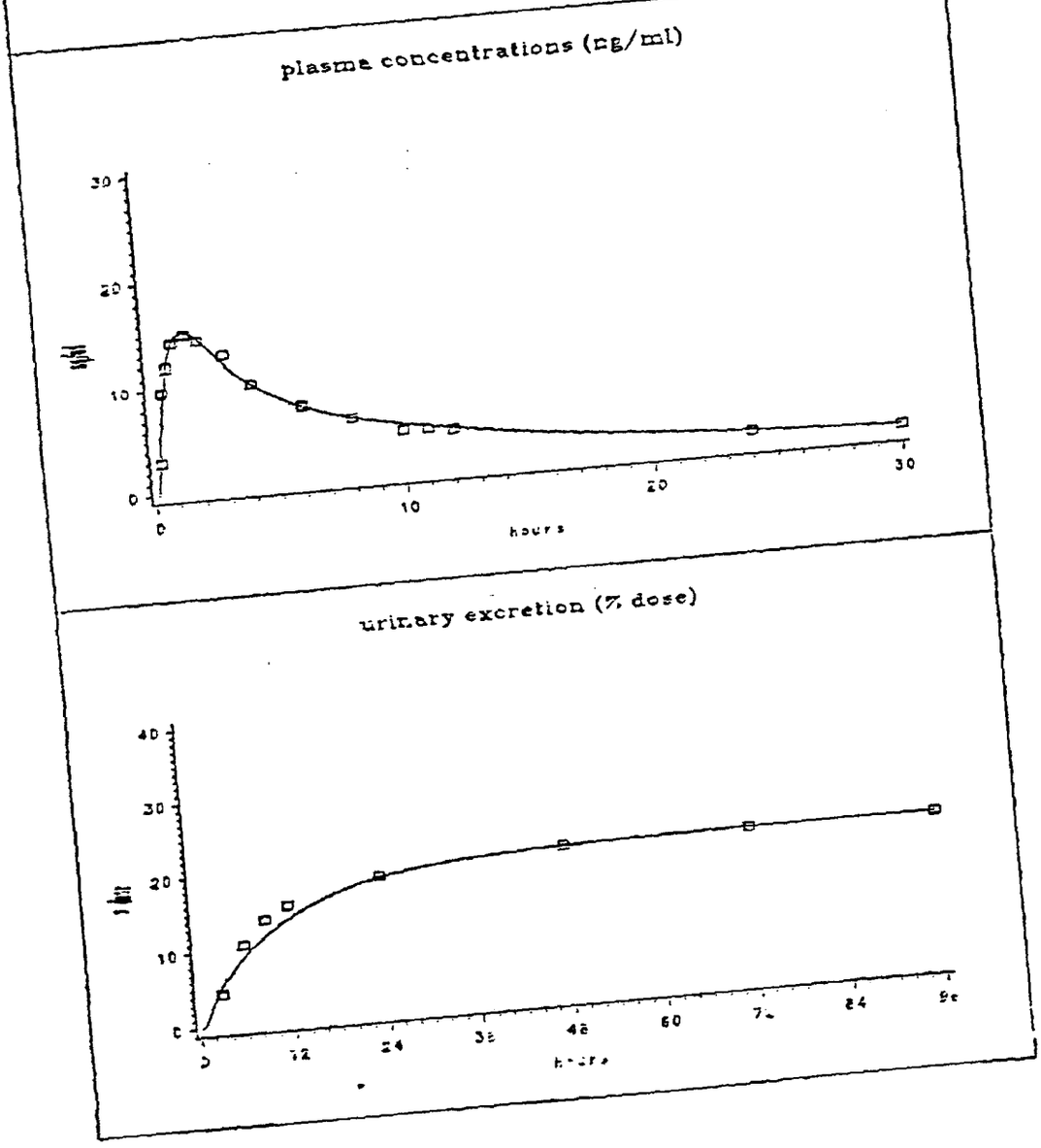


Fig 18 Mean curves of plasma concentrations and urinary excretion of WAL 801 CL (simulated from medians of kinetic parameters) and medians of experimental data
Oral dose 20 6 mg WAL 801 CL
Study No 640 011



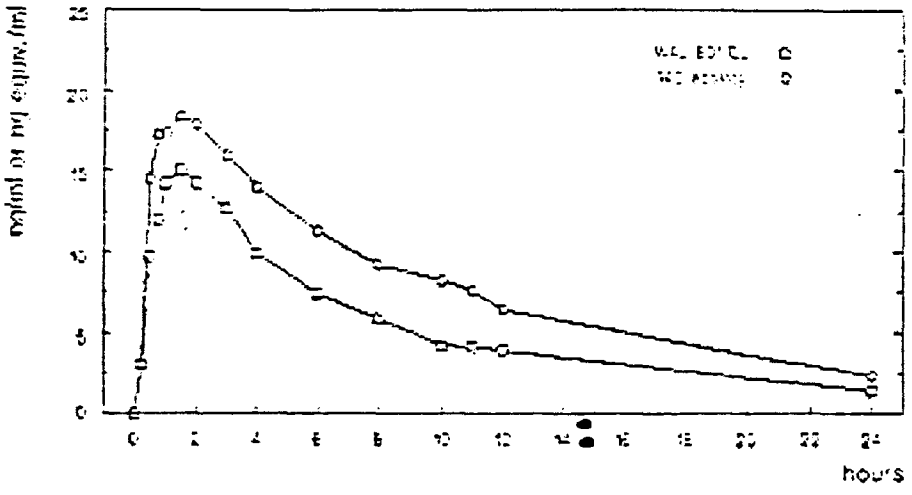


Fig 28: Medians of plasma concentrations of WAL 801 CL [ng/ml] and 14C activity [ng equiv./ml] after oral administration of 20.6 mg WAL 801 CL - 14C as aqueous solution

Study No: 640.011

The results of this trial indicates that epinastine is generally rapidly absorbed after oral dosing. That it is not metabolized to a great extent, even though it has affinity for some P-450 enzymes. Elimination is primarily through renal excretion, with the degree of renal excretion dependent upon route. With oral dosing a larger proportion of the drug appears in the stool, suggesting incomplete absorption. The absolute bioavailability of the oral solution based on plasma level or radioactivity was approximately 40%. Plasma protein binding, via equilibrium dialysis was approximately 65%, suggesting that it was not likely to participate in drug-drug displacement interactions in vivo.

Tab. 20A: Serum protein binding of WAL 801 CL-14C
Determination in triplicate by equilibrium dialysis
Initial concentration: c_c = 54.9 ng/ml (≙ 23042 dpm/ml)
Study No. 640.011

Subject	dpm/200 µl serum	dpm/200 µl buffer	$\bar{c}_{equ.}$*) [ng/ml]	bound %	mean % bound
1/			37.2	64.12	
				65.32	64.70
				64.66	
2/			36.8	62.26	
				61.48	62.15
				62.71	
3/			36.4	62.06	
				61.43	61.91
				62.25	
4/			35.9	60.41	
				60.69	60.80
				61.30	
5/			35.6	61.64	
				62.99	62.55
				63.01	
6/			38.9	70.62	
				71.06	70.76
				70.60	

*) $\bar{c}_{equ.}$ = mean serum concentration [ng/ml] at equilibrium

Although the previous study indicated quite convincingly that epinastine was not highly metabolized, the sponsor did provide the following article in the NDA in which the metabolic activity of epinastine and terfenadine are determined using in vitro methods.

METABOLISM OF EPINASTINE, A HISTAMINE H1 RECEPTOR ANTAGONIST, IN HUMAN LIVER MICROSOMES IN COMPARISON WITH THAT OF TERFENADINE

Wataru Kishimoto[1], *Toyoko Hirai*[1], *Kenji Sakai*[1], *Yoshihiko Funae*[2] *and Takashi Igarashi*[1]*

[1] Department of Drug Metabolism and Pharmacokinetics, Kawanishi Pharma Research Institute, Nippon Boehringer Ingelheim Co., 3-10-1, Yato, Kawanishi, Hyogo, 666-01, Japan

[2] Laboratory of Chemistry, Osaka City University Medical School, 1-4-54, Asahimachi, Abeno-ku, Osaka, 545, Japan

The metabolism of epinastine and terfenadine by human intestinal microsomes was also investigated. Epinastine did not yield any detectable amount of M-1 during incubation for 2 hours. However, terfenadine was metabolized into terfenadine alcohol, (not terfenadine acid,) with a Km value of 0.9 μM and a Vmax value of 84 pmol/min/mg protein.

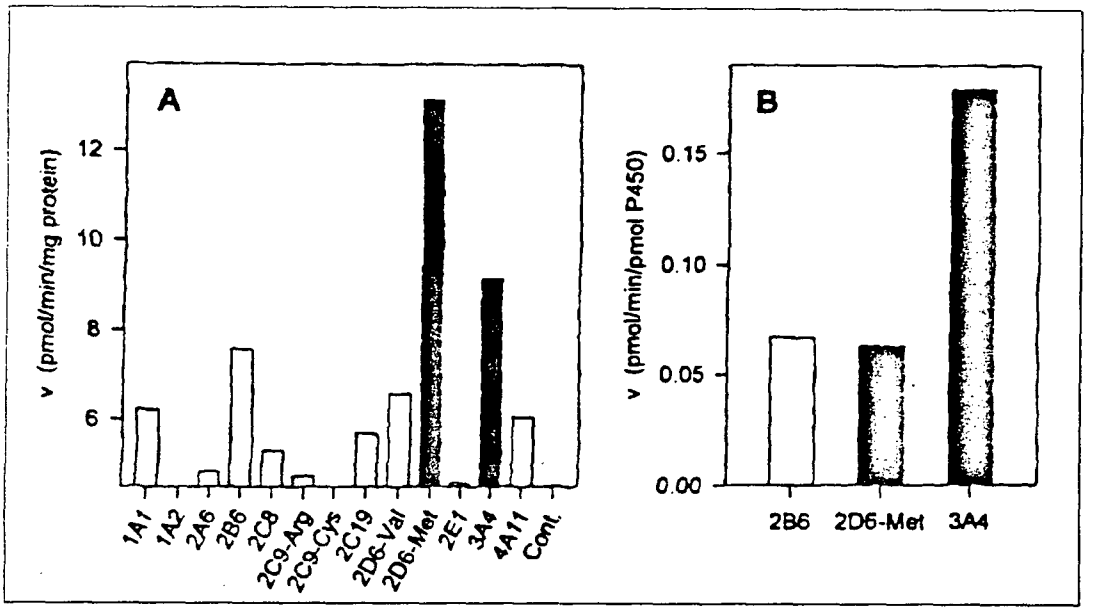
Metabolism of epinastine by recombinant CYPs : Metabolism of epinastine by microsomes expressing recombinant human CYPs (CYP1A1, 1A2, 2A6, 2B6, 2C9-Arg, 2C9-Cys, 2C19, 2D6-Val, 2D6-Met, 2E1, 3A4 and 4A11) and by microsomes from cells carrying the expression vector alone as a negative control was investigated. Epinastine metabolism was mainly catalyzed by three isoforms, i.e., CYP2D6-Met, 3A4 and 2B6 (Fig. 5A). CYP3A4 was a more efficient catalyst than 2D6-Met and 2B6 when the activity was expressed per P450 content (Fig. 5B). The apparent Km values for the formation of M-1 by CYP2D6-Met and 3A4 were 59.9 and 573.3 μM, respectively, which were similar to those obtained from Eadie-Hofstee plots with human liver microsomes, and intrinsic clearance (Vmax/Km) was greater for CYP2D6-Met than for CYP3A4 (Fig. 6). The activity of CYP2B6 were too low to allow calculation of the kinetic parameters. These results further support the idea that CYP2D6-Met and 3A4 are

the key enzymes that catalyze the metabolism of epinastine in human liver.

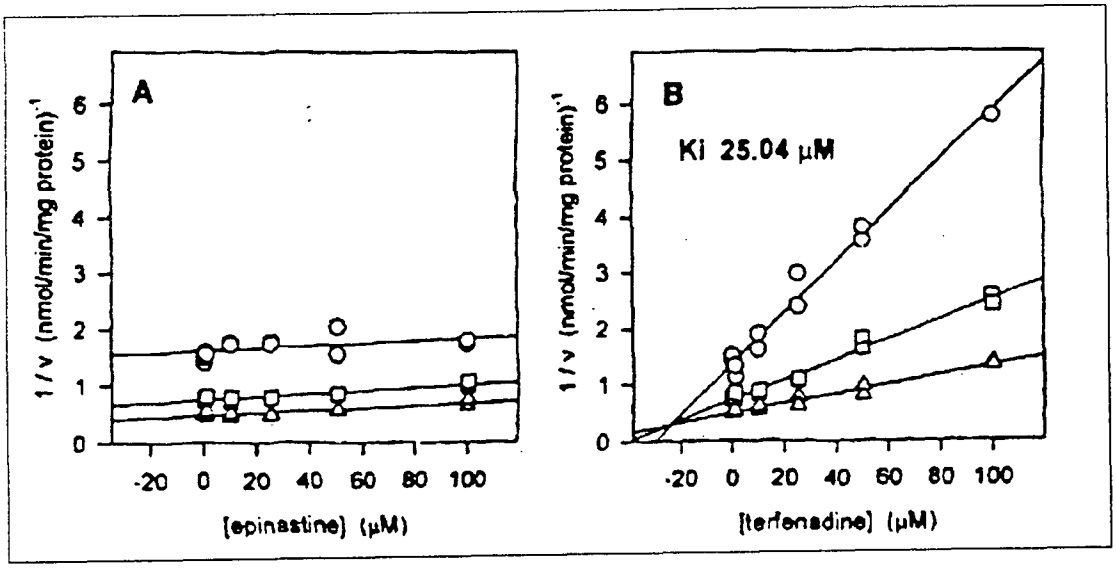
Table 1. Kinetic parameters for epinastine metabolism and terfenadine carboxylation in human liver microsomes.

	Km (μM)	Vmax (pmol/min/mg)	Vmax/Km
Epinastine	232.2 ± 120.7	200.5 ± 121.9	0.832 ± 0.19
Terfenadine	1.78 ± 1.00	173.8 ± 75.1	103.9 ± 18.9

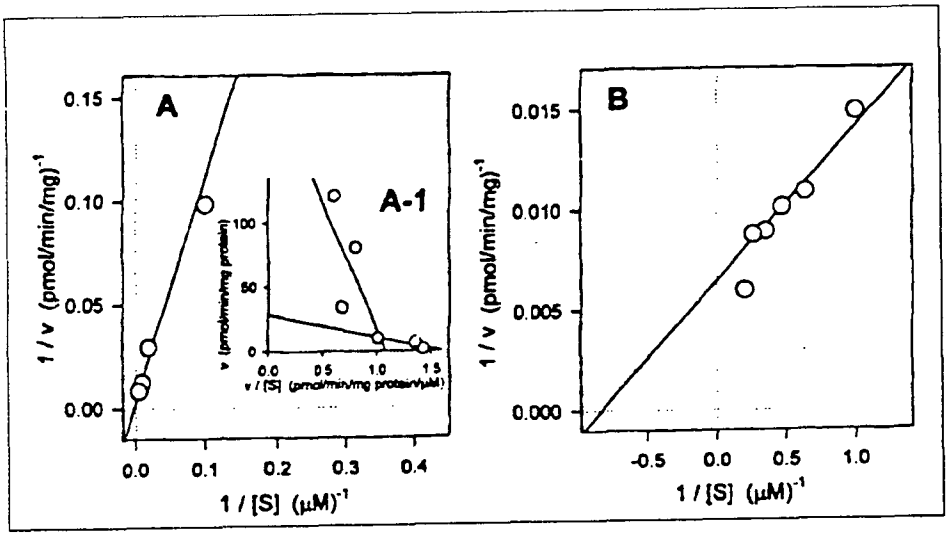
Values are mean ± S.E.
Liver samples used were HHM0195, 0223 and 0224.



Metabolism of epinastine by specific human CYPs expressed in microsomes of B-lymphoblastoid cells. Metabolic activities (v) were represented as per mg protein (A) and per pmol P450 content (b)



Dixon plots of the effects of epinastine (A) and terfenadine (B) on testosterone 6β-hydroxylation by human liver micsrosomes (HHM0223) at 50(triangles), 100(square), and 250(circle) µM testosterone.



Typical Lineweaver-Burk plots for epinastine metabolism (A) and terfenadine metabolism (B) by human liver microsomes.
The concentration range of epinastine and terfinadine were 1-200 UM and 1-5UM, respectively. The insert in figure A is the Eadie-Hofstee plot of M-1 formation. Lines were fitted by leasts squares linear regression.

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