CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-127

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-127 SUBMISSION DATE: 8/5/99, 9/2/99, 12/2/99

PRODUCT: Azelastine Hydrocholoride ophthalmic solution, 0.05%

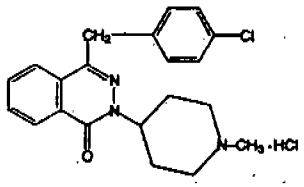
SPONSOR: Asta Medica
Tewksbury, MA 01876

REVIEWER: Veneeta Tandon, Ph.D.

NDA Review

I. BACKGROUND

Drug Classification: 3S
Dosage Form: Solution (0.5 mg/ml)
Indication: Prevention and relief of signs and symptoms of allergic conjunctivitis in adults and children (4 years and older).
Drug Class: Antihistamine (H_1 antagonist). Azelastine Hydrochloride has the following chemical structure.



Dose and administration: One drop per eye twice a day at an interval of 8-10 hours.
Foreign Marketing History: Azelastine Eye drops are approved for use in adults in various European countries. Azelastine HCl in nasal spray (Astelin®) is approved in the US since November 1996 (N20-114; Wallace Laboratories) and in other countries for the treatment of allergic rhinitis. The recommended dose is two sprays (0.28 mg) per nostril twice daily. The oral form is approved in other countries for the treatment of allergic rhinitis and asthma at a recommended dose of 2.2 to 4.4 mg twice daily.

Formulation:

Ingredient	Quantity (mg/bottle)
Azelastine hydrochloride	[redacted]
Benzalkonium chloride	
Hydroxypropylmethyl cellulose	
Disodium edetate dihydrate	
Sorbitol solution (70%)	
Sodium hydroxide (1N)	
Water for injection	

II. ANALYTICAL VALIDATION

[redacted]

III. PHARMACOKINETIC STUDIES

The sponsor has conducted one study in patients under maximum exposure condition to evaluate the systemic availability of AZE upon administration of topical azelastine eye drops. The pharmacokinetics of azelastine following oral and nasal administration has been evaluated under NDA 20-114 and the sponsor has provided right of reference from Wallace laboratories for these studies. Since these studies have been reviewed in October 1995, they will not be summarized again. Only the study conducted using topical azelastine eye drops has been reviewed here.

Study number 2983: A multi-center, placebo-controlled, parallel-group, double-blind environmental study to evaluate safety and efficacy of azelastine eye drops in adult patients with seasonal allergic conjunctivitis/rhinoconjunctivitis (Phase III Study).

Clinical Site
Dr. L.A. Gorjakina (4 sites)
Moscow, Russia

Analytical Site
Asta Medica AG
Frankfurt, Germany

Study Population: A total of 277 patients (114M & 163 F) with a history of allergic conjunctivitis, between the ages of 18-64 years participated in this study.

Treatment: Patients were treated with either azelastine eye drops (1 drop/eye b.i.d equivalent to 0.06 mg azelastine HCl, batch no. 44603) or placebo (batch no. 43602) for 8 weeks. If necessary, the number of applications could be increased to 3-4/day. The total daily doses ranged from 0.06-0.12 mg of azelastine (0.03 mg of AZE/ocular dose). There was a 1-week follow-up post last administration of study drug.

Plasma sampling: The sponsor evaluated the systemic bioavailability of AZE in a subset of patients (N=30) from this study at two study sites.

At site 1, samples from 20 patients were collected prior to study drug administration (Day 0, Visit 1) and at Day 14 or Visit 3 (at 4-5 hours after the last dose) and Day 56 or Visit 5 (at 12-15 hours after the last dose).

At site 4, samples from 10 patients were taken on Day 56 prior to and two hours following the final administration of the study drug. Plasma levels of AZE and its main metabolite N-desmethyl-AZE were determined.

Out of the 30 patients, whose blood samples were taken, 23 were on the active treatment and 7 on placebo (11 AZE and 5 placebo on Day 14 and 9 AZE and 1 placebo on Day 56).

Systemic Bioavaliability

Azelastine plasma levels: Plasma levels of AZE were either not detectable or below the limit of quantitation in all except one patient in Center 1 (1/23). The plasma level observed for this patient was [redacted] No levels were quantifiable after 8 weeks of treatment in this subject. No patients at Center 4 had detectable AZE plasma concentrations.

N-desmethyl-azelastine plasma levels: Plasma levels of the main metabolite N-desmethyl-AZE were detected in 2/11 patients (plasma level between [redacted]) in Center 1, and in 3/9 patients in Center 4. Out of these three subjects one subjects was on placebo. The sponsor has not given any explanation for this. There was no relation to the time distance between collecting samples.

Subject number 23 from Center 1 had plasma levels of both AZE and its metabolite. He was a 46 year old Caucasian male. This patient also had desmethyl-AZE concentrations prior to treatment.

It has been reported the review of NDA 20-114 that the desmethyl-AZE has equal activity as compared to the parent drug. This metabolite has a half-life of 54 hours compared to 22 hours for the parent drug.

Assay results showing azelastine and desmethyl-azelastine concentrations are shown in the following Tables on pages 4-6.

Table1:
Assay results Azelastine and Desmethylazelastine (ng/mL): A-05610-2983 Centre 1

Subject No.	Round No. (*1)	Treatment (*2)	Concentr. Azelastine (*3)	Concentr. Desmethyl-azelastine
A 19	1	no	ND	ND
P 20	1	no	ND	ND
P 21	1	PLA	ND	ND
P 21	3	PLA	ND	blq
P 21	5	PLA	ND	ND
A 23	1	AZE	blq	0.56
A 23	3	AZE	0.29	0.87
A 23	5	AZE	blq	blq
A 24	1	AZE	ND	ND
A 24	3	AZE	blq	0.25
A 24	5	AZE	ND	0.7
P 25	1	PLA	blq	ND
P 25	3	PLA	ND	ND
P 25	5	PLA	ND	ND
A 27	1	PLA	ND	ND
A 28	1	AZE	ND	ND
A 28	3	AZE	blq	ND
A 29	1	AZE	blq	ND
A 29	3	AZE	blq	ND
A 29	5	AZE	blq	ND
P 30	1	PLA	blq	ND
P 30	3	PLA	blq	ND
P 30	5	PLA	blq	ND
A 31	1	AZE	blq	ND
A 31	3	AZE	blq	ND
A 31	5	AZE	blq	ND
A 32	1	AZE	ND	blq
A 32	3	AZE	blq	ND
A 32	5	AZE	ND	blq

(*1): Round 1: sampling prior to treatment; Round 3: sampling after a 14-days treatment; Round 5: sampling after an 8-weeks treatment
(*2) AZE: Azelastine
PLA: Placebo
(*3): ND: not detectable
blq: below the limit of quantification

Table 1 continued:

Assay results Azelastine and Desmethylazelastine (ng/mL): A-05610-2983 Centre 1

Subject No.	Round No. (*1)	Treatment (*2)	Concentr. Azelastine (*3)	Concentr. Desmethyl-azelastine
P 33	1	PLA	ND	ND
P 33	3	PLA	ND	blq
P 33	5	PLA	ND	ND
A 34	1	AZE	ND	ND
A 34	3	AZE	ND	ND
A 34	5	AZE	ND	blq
A 35	1	AZE	blq	blq
A 35	3	AZE	blq	blq
A 35	5	AZE	blq	blq
A 36	1	AZE	blq	blq
A 36	3	AZE	blq	ND
A 36	5	AZE	blq	blq
P 37	1	PLA	blq	ND
P 37	3	PLA	blq	ND
P 37	5	PLA	ND	ND
A 38	1	AZE	blq	ND
A 38	3	AZE	blq	ND
A 38	5	AZE	blq	ND
A 39	1	AZE	blq	blq
A 40	1	AZE	ND	ND
A 40	3	AZE	blq	ND
A 40	5	AZE	blq	ND

(*1): Round 1: sampling prior to treatment; Round 3: sampling after a 14-days treatment; Round 5: sampling after an 8-weeks treatment

(*2) AZE: Azelastine
PLA: Placebo

(*3): ND: not detectable
blq: below the limit of quantification

Table 2:

Assay results Azelastine and Desmethylazelastine (ng/mL): A-05610-2983 Centre 4

Subject No.	Blood sampling No. (*1)	Treatment (*2)	Concentr. Azelastine (*3)	Concentr. Desmethyl-azelastine
219	1	AZE	ND	ND
219	2	AZE	blq	ND
223	1	AZE	blq	ND
223	2	AZE	blq	ND
228	1	AZE	blq	blq
228	2	AZE	blq	blq
230	1	AZE	ND	0.3
230	2	AZE	ND	0.27
232	1	AZE	ND	0.43
232	2	AZE	blq	0.37
237	1	AZE	blq	ND
237	2	AZE	blq	ND
242	1	AZE	blq	ND
242	2	AZE	blq	blq
243	1	AZE	ND	ND
243	2	AZE	blq	ND
247	1	AZE	blq	ND
247	2	AZE	blq	ND
273	1	PLA	ND	0.36
273	2	PLA	ND	0.36

(*1): sampling after an 8-weeks treatment
Round 1: sampling immediately before the last administration;
Round 2: sampling 2 hours after the last administration

(*2) AZE: Azelastine
PLA: Placebo

(*3): ND: not detectable
blq: below the limit of quantification

APPEARS THIS WAY
ON ORIGINAL

IV. OVERALL CONCLUSIONS

The systemic bioavailability of azelastine eye drops is poor after 8 weeks of treatment. Only 1 patient had detectable levels of AZE after 14 days of treatment. 2 out of 11 patients had detectable levels of desmethyl-AZE after 14 days of treatment and 4 out of 19 patients had detectable levels of desmethyl-AZE after 56 days of treatment.

The maximum recommended dose of azelastine eye drops is 0.06 mg/day for the treatment of allergic conjunctivitis as compared to the maximum recommended dose of 1.12 mg/day for intranasal azelastine and 8.8 mg/day of oral azelastine for the treatment of allergic rhinitis. Hence the ophthalmic dose is about 18-140 folds lower than the intranasal/oral dose. The pharmacokinetics of azelastine after intranasal/oral administration has been reviewed under NDA 20-114 and hence not described again in this review.

V. RECOMMENDATION

The reviewer recommends approval of the application from biopharmaceutics standpoint. There are no comments regarding the application. A copy of the sponsor's label is attached and the pharmacokinetics section of the label is adequate.

/S/ 12/15/99

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Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. /S/ 12/15/99

CC: NDA 21-127
HFD-550/Div File
HFD-550/CSO/Rodriguez
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

4 page(s) of revised draft labeling has been redacted from this portion of the review.