CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-816

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 4 1997

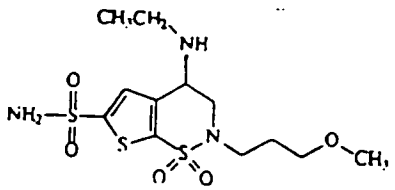
Clinical Pharmacology/Biopharmaceutics Review

NDA:	20-816	SUBMISSION DATE: Jan 28, 1997
PRODUCT:	Brinzolamide Ophthalmic Suspension 1% AZOPT™	
SPONSOR:	Alcon Laboratories Ft. Worth, Tx.	REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

I. Background

AZOPT™ 1% is a sterile aqueous suspension of brinzolamide, a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. It is intended for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Brinzolamide ophthalmic suspension 1% has not been registered or marketed in any country outside the United States. Marketing applications are also not pending approval in any other country at this time. The applicant is seeking approval of it with 2-3 times daily dosing of one drop of AZOPT™ to the affected eye.



Brinzolamide is chemically described as: (R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e]thiazine-6-sulfonamide-1,1-dioxide. It is a white to off white powder, which is insoluble in water and slightly soluble in methanol and ethanol. It has a molecular weight of 383.5 and a melting point of about 131°C.

II. Recommendation

The sponsor has submitted results of two topical multiple dose study and one study using oral dosing. Out of these three studies, only the first 15 day topical dosing study is complete. A 9 month interim report is provided of the 18 month long term topical study. Wash out results from the oral study is also yet to be completed. No

urinary excretion results have been provided so far, though the sponsor has mentioned in the label that brinzolamide is eliminated predominantly in the urine as unchanged drug and that N-Desethyl brinzolamide is also found in the urine along with lower concentration of N-desmethoxypropyl and O-desmethyl metabolites.

Brinzolamide is absorbed systemically following topical ocular administration and distributes to sites containing CA. Concentrations in plasma are low with levels in human after topical administration (3% TID 2 weeks) below the assay quantitation limit Plasma levels after oral administration of 1 mg BID were mainly below quantitation limits with intermittent values approximately In blood brinzolamide distributes almost entirely into RBCs due to its high affinity for CA II, leading to saturation of this isoenzyme in RBCs upon repeated dosing. As a consequence of saturable binding the pharmacokinetics of brinzolamide is nonlinear and dose proportionality is generally not observed. This also contributes to a long whole blood half life of 111 days. Brinzolamide is well tolerated in humans. In general, the pharmacokinetic requirements have been met in this NDA. There are, however, a few comments that need to be addressed by the applicant prior to approval. (see comments 1-6, pages 13&14).

INDEX

I.	Background * * * * * * *	1
II.	Recommendation * * * * * *	1
III.	PK Studies Overview * * * * * *	3
IV.	Formulations * * * * * * *	3
V.	Special Population * * * * * *	4
VI.	Analytical Methods * * * * * *	4
VII.	Topical Ophthalmic dosing * * * * *	6
VIII.	Oral Dosing * * * * * * *	9
IX.	Protein Binding * * * * * *	12
X.	Conclusions * * * * * * *	12
XI.	Comments * * * * * * *	13

Appendix I- Studies

Study #	Short Summary Title	Page No
Topical Ophthalmic studies		
C-92-34	Multiple dose study of 3% brinzolamide ophthalmic suspension in normal male volunteers for 14 days	2
C-95-47	Multiple dose long term study (18 months) of 1% brinzolamide ophthalmic suspension in patients	10

Oral Studies

C-95-76	Multiple dose study of 1 mg capsules of brinzolamide in normal volunteers for 32 weeks	19
In Vitro Studies	In vitro plasma protein binding	30

III. PK Studies Overview

The applicant has conducted trials using both topical ophthalmic and oral dosing of brinzolamide. Contained as part of this application is a request for a waiver of in vivo bioavailabilty studies in human. The section cited by the applicant, however is specific to inhaled anesthetic agents and as such is not applicable. However, the applicant has conducted trials comprising of topical application of brinzolamide 1% for two weeks and 18 months (ongoing). This information in combination with additional pharmacokinetic information from the oral route of administration should be sufficient for approval.

The clinical pharmacokinetics of brinzolamide have been investigated in two topical ocular studies and one oral study. The phase I studies include a safety study (C-92-34) of 15 days duration in normal volunteers and an oral PK study (C-95-76) for 32 weeks duration plus a 12 week washout in normal volunteers. The washout part of the study is ongoing. Evaluation of urinary excretion at steady state is in progress. Phase III study in patients includes a topical long term study (C-95-47) of 18 months duration. Interim report for upto 9 months has been submitted in this NDA.

IV. Formulations

The proposed market formulation and that used the studies is given below:

Ingredient	Drug Product	Protocol C-92-34	Protocol C-95-47
Brinzolamide			
Mannitol			
Tyloxapol			
Sodium Chloride			
Edetate Disodium			
Benzalkonium Chloride			
NaOH and/or HCl to pH			
Purified Water			

V. Special Populations

Brinzolamide was studied in both males and females in topical and oral studies with an age range of 18-70. However, the age effect on drug and metabolite concentrations were not evaluated.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

VII. Topical Ophthalmic dosing

The sponsor has presented two studies from ophthalmic dosing using similar protocols.

Study # (C-92-34) : *Safety of topical AL-4862 3% suspension dosed TID in normal volunteers for 15 days.*

In this study, concentrations of AL-4862 were measured in plasma and whole blood following multiple topical ocular dosing. Fifteen normal volunteers were administered 1 or 2 drops of 3% AL-4862 ophthalmic suspension bilaterally for 14 days, plus one dose on the morning of day 15. Blood and plasma samples were obtained 2 hours after morning doses (approximate Cmax) of days 8 and 15 (last dose), and approximately every other week for the next 8 weeks. The extended sampling was designed to monitor the anticipated long life of AL-4862 in erythrocytes. It is to be noted here that this formulation of AL-4862 was stronger than that proposed for marketing (i.e. 1%). The purpose of this investigation was to evaluate, for the first time in humans, the ocular and systemic safety of topically applied 3.0 % AL-4862 as an ophthalmic suspension. Results from this study are shown in the Appendix on pages 2-9.

Whole blood and plasma levels of drug and metabolite: After 8 days of TID dosing with AL-4862 ophthalmic suspension 3%, the mean whole blood concentration 2 hours after 8.00 a.m. dose was 1.42 ± 0.80 μg/mL). After two week of dosing the maximal concentration increased approximately 1.5 fold to 2.17 ± 0.85 μg/mL The whole blood levels of AL-4862 declined over the next 8 weeks with a mean half life of 111 ± 29 days. The AUC (0-∞) was 334±120 μg.day/mL. AL-4862 was not detectable in plasma The drug was sequestered in the erythrocytes bound to CA. AL-4862 was not at whole blood steady state after 15 days of TID dosing. The results are shown in the Appendix as pages 5-7.

IOP reduction: Minimal IOP reductions were seen, which not be unexpected in normal population of subjects. Mean IOP decreased up to 2.1 mmHg throughout the diurnal observations on study day 1. On days 3, 8, and 15 mean IOP was reduced 0.8, 0.2 and 0.5 mmHg, respectively. The mean IOP change from baseline by visit is attached in the Appendix as pages 8-9.

Dropouts: There were two drop outs in the study (#108 and 109). # 108 discontinued for noncompliance and # 109 discontinued for adverse experience (Edema of the lid on day three and contact dermatitis on day 8). Patient #109 was rechallenged with the usual dose with the same symptoms occurring again to a milder extent.

Drug Interactions: Concomitant medications used in the study included acetaminophen. No drug-interactions were noted.

Adverse effects: AL-4862 ophthalmic suspension 3% was evaluated for safety in 15 normal adult subjects. Adverse effects related to AL-4862 treatment was nonserious, usually resolved without treatment and did not result in sequelae. Ocular precipitate (drug residue) (46.7%) and foreign body sensation (26.7%) were the most frequently reported treatment related to ocular events and taste perversion (80%) was the frequently reported nonocular event. There were no clinically significant changes noted in visual acuity, pulse or mean arterial pressure.

Comments

(1) Since the sponsor has used sex of the patient and week as parameters in the statistical analysis in the other oral dosing study, it would have been ideal to do this study in the same kind of population, i.e., including both males and females, also including both Caucasians and blacks in the study.

(2) Carbonic anhydrase inhibition has not been studied in this protocol.

Study # (C-95-47): *A twelve month, multicenter, triple masked, parallel study of the efficacy and safety of BID and TID dosed AL-4862 1% ophthalmic suspension compared to BID dosed timolol 0.5% in the treatment of patients with primary open angle glaucoma or ocular hypertension.*

In this study brinzolamide (AL-4862) and N-desethyl brinzolamide (AL-8520) RBC concentrations and carbonic anhydrase activities (total and CA II isoenzyme) in RBCs were determined from a long term study (18 months) of brinzolamide 1% ophthalmic suspension (TID and BID) in patients with primary open angle glaucoma or ocular hypertension. This report presents interim data for all patients for which at least 6 months data is available. Few patients have been analyzed up to the first 9 months. The results from these studies are presented in the Appendix on pages 10-18.

Whole blood levels of drug and metabolite: Topical ocular administration of brinzolamide 1% results in systemic exposure of the drug. Quantifiable Brinzolamide concentrations were seen by month 3. The concentrations were near or slightly above 20 μM, which is the approximate concentration expected to give saturation of the CA II isoenzyme in blood. The concentration was higher in case of TID dosing. By month 6, nearly half of the BID group patients (9 out of 19) and two-thirds (10 out of 15) of the TID patients showed RBC parent drug concentrations close to or above 20 μM (CA II saturation). At 9 months, 6 out of 8 patients for whom data was available had achieved or were within about 90% of CA II saturation. The study is completed for 6 months in most patients. There was high inter subject variability in both treatment groups.

The metabolite N-desethyl brinzolamide (AL-8520) concentrations were below limit of quantification None of the BID and only 3 out of 15 TID patients

had quantifiable limits of the metabolite at 3 months. Metabolites AL-4830 and AL-5859 were not observed in humans. There were only slight increases between 6 and 9 months for the parent drug, while the metabolite concentrations continued to increase. TID treatment exhibited higher RBC levels of metabolite and parent drug. Since the study is not complete, confirmation of steady state cannot be made. The results are shown in the Appendix on pages 13-14.

Mean interim RBC μM concentrations of brinzolamide and N-desethyl brinzolamide with the standard deviations are summarized below:

BID Treatment

	3 months		6 months		9 months	
	brinzolamide	AL-8520	brinzolamide	AL-8520	brinzolamide	AL-8520
Mean	13.4 ± 5.7	BLQ	18.7 ± 5.2	BLQ	19.3 ± 3.4	1.5 ± 1.0
N	12	12	13	13	8	8

TID Treatment

	3 months		6 months		9 months	
	brinzolamide	AL-8520	brinzolamide	AL-8520	brinzolamide	AL-8520
Mean	15.0 ± 8.2	BLQ	19.2 ± 7.8	2.68 ± 3.31	21.3 ± 10.2	7.96 ± 7.59
N	15	15	15	15	5	5

Based on inspection of individual concentration data, the time required to saturate RBC CA II with BID and TID topical dosing appears variable, ranging from 3 to perhaps 12 months in few cases. The majority of subjects appear to be reaching RBC concentrations of brinzolamide sufficient to saturate CA II by 6 to 9 months. In contrast 1 mg brinzolamide administered orally BID resulted in CA II saturation within 2-4 weeks, indicating a much lower rate of systemic input by the topical route.

Plasma levels of drug and metabolite: Plasma levels of drug and metabolite have not been determined for this study.

IOP reductions: Efficacy data has not been presented.

Total CA and CA II activity: CA II activity showed a higher relative decrease on average compared to the total activity. This is expected due to preferential binding of the drug to CA II. The results have been summarized in the tables below:

BID Treatment

	3 months		6 months		9 months	
	Total CA activity	CA II activity	Total CA activity	CA II activity	Total CA activity	CA II activity
Mean	54.4 ± 19.9	35.6 ± 25.9	43.5 ± 15.2	21.8 ± 19.2	44.9 ± 10.7	16.2 ± 10.3
N	11	11	12	12	7	7

TID Treatment

	3 months		6 months		9 months	
	Total CA activity	CA II activity	Total CA activity	CA II activity	Total CA activity	CA II activity
Mean	54.5 ± 23.9	34.9 ± 35.7	47.0 ± 22.3	25.5 ± 31.4	49.4 ± 21.1	23.0 ± 35.6
N	13	13	13	13	4	4

The data shows the high inter patient variability as reflected by the standard deviations. There is a higher relative decrease in case of CA II activity, because of the selectivity of the drug for CA II isoenzyme. This variability is also reflected in the drug and metabolite levels. The maximum degree of total inhibition observed thus far in the study is 40-70% in about 9 months. This is well below the > 99% inhibition associated with adverse systemic side effects. Total CA inhibition appears to be leveling off between 3 and 6 months, indicating an approach to pharmacodynamic steady state. The results are shown in the Appendix on pages 15-18.

Due to much lower rate of systemic drug input by topical route relative to oral administration, steady-state drug plus metabolite RBC concentrations will be lower than that seen in the oral study. A strong positive correlation is evident between % CA inhibition and RBC drug plus metabolite concentrations up to about 20 μM RBC concentration. At this point CA II is saturated.

Comments

(1) Since this is an interim report, there is not much information provided to meet the objectives of the study, hence no conclusions can be made.
(2) No statistical comparison has been done between the BID and TID dosing due to the high inter-subject variability.
(3) Once again the sponsor has neglected the urine analysis in terms of amount of drug and metabolite excreted.
(4) No preliminary information is given on corneal thickness and endothelial cell count.
(5) No information has been provided about the drug lot number used for the study.

VIII. **Oral Dosing**

Study # C-95-76 : *A double-masked, parallel group, placebo-controlled, multiple-dose, pharmacokinetic study of AL-4862 following oral dosing in normal volunteers.*

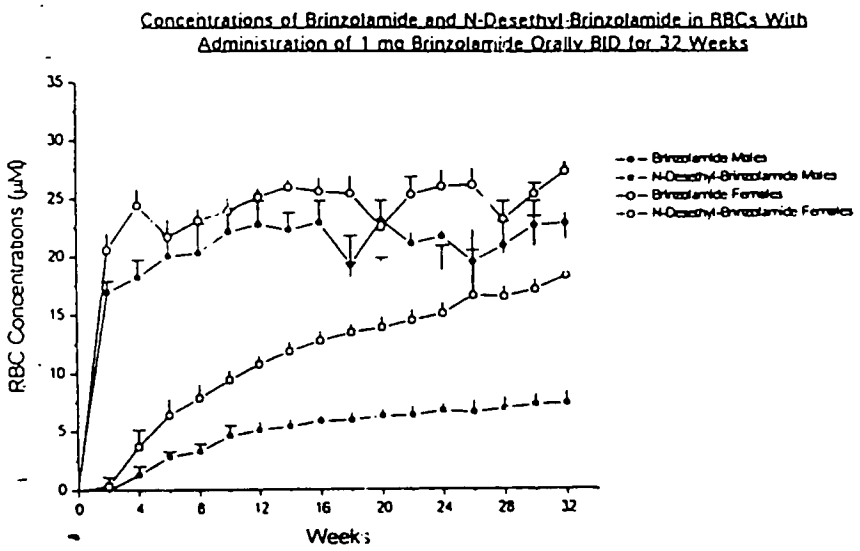
14 subjects on active drug (7males/7 females) completed the study and provided the pharmacokinetic and red blood cell carbonic anhydrase activity results. The subjects were randomized into one of the two treatment groups (1mg of brinzolamide BID or placebo BID) in a 4:1 ratio in favor of the brinzolamide treatment arm. The results of this study are shown in the Appendix on pages 19-26.

Whole Blood levels of drug and metabolite: Brinzolamide was readily absorbed following BID oral administration of 1 mg doses with RBC CA II saturation occurring at

a concentration of about 20 μM within 2-4 weeks as opposed to 6-9 months after topical dosing. Steady-state levels of parent drug in RBCs was achieved within approximately 12 weeks at a mean concentration of 20-25 μM. Analysis of variance for RBC concentrations of brinzolamide indicated significant sex, week and sex by week interactions. For females steady-state was achieved by week 12 and for males steady-state was achieved by week 10. At week 32, mean parent drug RBC concentration were 22.7 ± 2.4 μM in males and 27.1 ± 1.3 μM in females.

The O-desethyl and N-desmethoxypropyl metabolites found in animals were not detected in human blood. Quantifiable RBC concentrations of N-desethyl metabolite (AL-8520) were present in all subjects by week 6. N-desethyl metabolite exhibited binding to CA I and reached steady state between 20-28 weeks. Analysis of variance for RBC concentrations of N-desethyl brinzolamide indicated significant sex, week and sex by week interactions. Among females, steady-state for N-desethyl brinzolamide had been achieved by week 26 and among males steady-state had been achieved by week 24. Sex difference was greater for metabolite than for parent drug. At week 32, mean N-desethyl metabolite RBC concentration were 7.31 ± 1.82 μM in males and 18.2 ± 7.5 μM in females. Detailed results are shown in the Appendix on pages 22-23.

The concentration of drug and metabolite in RBCs is shown in the figure.



Plasma levels of drug and metabolite: Over the 12 hour period following initial dose, plasma drug concentrations were below the quantitation limit with intermittent samples exhibiting levels At week 16, quantifiable brinzolamide concentrations were found in 28 of 105 samples. For exit plasma data, only 31 out of 98 samples had quantifiable drug concentrations. Results are shown in the Appendix on page 24. No detectable amounts of N-desethyl brinzolamide plasma concentrations were found in any subject over the course of the study. Due to very

limited number of quantifiable drug concentrations, no pharmacokinetic analysis of the plasma data was performed. Low plasma concentrations, relative to whole blood, are expected due to tight binding of CAIs to erythrocyte carbonic anhydrase.

Total CA and CA II activity: Pharmacodynamic steady-state for RBC total CA and CA II activity was achieved by week 4. The mean total CA inhibition of about 70% was well below that associated with adverse systemic side effects. By week 4, total CA activity ranged from approximately 21-35% of baseline and remained relatively constant over rest of the dosing regimen. CA II activities decreased to about 4-5% by week 4. No sex related differences in either total CA or CA II activities were evident. Results are summarized in the Appendix on pages 25-26.

Drop outs: Three subjects discontinued from the study due to paresthesia, chest pain , dizziness.

Drug Interactions: Concomitant administration of nonsteroidal anti-inflammatory agents and anti-allergic agents showed no untoward reaction in the subjects.

Safety assessment: categorized as below:

Ocular events related to therapy: mild lid spasm (5%)
Nonocular events related to therapy: headache(30%), paresthesia(20%), diarrhea(10%), fever(10%), others(5%)
Ocular events not related to therapy: burning, ocular pruritis, contact lens film blurred vision. 2 subjects
Nonocular events not related to therapy: headache(25%), rhinitis(20%), others (15%)

Overall conclusion was that brinzolamide was safe and well tolerated in normal, healthy subjects. Adverse events were nonserious, mild to moderate, usually resolved without treatment and did not interrupt continuation in the study.

Comments

(1) This report does not include data from the 12 week washout phase which was performed for the characterization of brinzolamide and N-desethyl brinzolamide elimination kinetics after the exit visit. The report will be ammended when results are available. Data is not available for the variance of the plasma and whole blood concentrations of brinzolamide and its metabolites, hence a confidence interval width, and power of the treatment comparison has not been stated by the sponsor. Serum creatinine results have not been reported yet.
(2) A discrepancy is noted in the instruction to the patient regarding the duration of fasting prior to the examination. The patient is instructed to fast for 2 hours prior to the week 2, 4, 10, 12, 14, 18, 20, 22, 26, 28, 30, exam and to fast at least 10 hours prior to their week 8, 16, 24, 34.
(3) No pharmacokinetic parameters were able to be calculated.

IX. Protein Binding

In vitro protein binding of ^{14}C-AL4862 has been studied in human, rat and monkey plasma by ultrafiltration over a concentration range of 0.01 to 10.0 μg/g. ^{14}C-AL4862 was found to be moderately bound to all three species. The binding of ^{14}C-AL4862 to human plasma protein was 62.7 to 58.8% over the range 0.01 to 10 μg/g indicating concentration independence. In rat and monkey plasma, the binding was elevated at the 0.01 μg/g level, but concentration independent from 0.1 to 10 μg/g. Excluding the 0.01 μg/g level, the binding was 79.9% to 74.8% in monkey plasma and 28.5% to 23.8% in rat plasma. The moderate extent of plasma protein binding of AL-4862 is not considered likely to result in drug interactions. The summary of the results is shown below.

Species	Mean Percent bound (n=5) ± SD			
↓ Conc →	0.01 μg/g	0.1 μg/g	1.0 μg/g	10 μg/g
Human	62.7 ± 1.6	59.1 ± 1.4	58.5 ± 0.2	58.8 ± 1.4
Monkey	95.5 ± 0.9	79.9 ± 0.3	75.4 ± 0.2	74.8 ± 0.3
Rat	40.3 ± 0.9	28.5 ± 1.1	24.3 ± 0.2	23.8 ± 0.4

X. Conclusions

- Brinzolamide is absorbed systemically following topical ocular administration and distributes to sites containing CA. Concentrations in plasma are low with levels in human after topical administration (3% TID 2 weeks) below the assay quantitation limit Plasma levels after oral administration of 1 mg BID were mainly below quantitation limits with intermittent values
- In blood brinzolamide distributes almost entirely into RBCs due to its high affinity for CA II, leading to saturation of this isoenzyme in RBCs upon repeated dosing. As a consequence of saturable binding the pharmacokinetics of brinzolamide is nonlinear and dose proportionality is generally not observed. This also contributes to a long whole blood half life of 111 days.
- Compound is moderately bound to plasma proteins
- Brinzolamide is metabolized to N-desethyl, N-desmethoxypropyl and O-desmethyl metabolites in animals. N-desethyl brinzolamide is the only metabolite detected in humans following topical and oral administration. This compound too distributes into RBCs, but appears to associate more with CA I.
- Following oral administration of 1 mg capsules twice a day, brinzolamide accumulates after 2-4 weeks to concentrations in the RBC which saturate CA II (~ 20 μM). N-desethyl brinzolamide approaches steady state after 20-28 weeks.
- In an oral study, CA II was inhibited by about 95-96% and total CA by approximately 70% at steady state. This level of CA inhibition is not sufficient to produce the systemic pharmacological side effects associated with oral CAIs.

- Gender differences were evident in concentrations of the N-desethyl metabolite from oral study. Steady state RBC concentrations were approximately 7μM in males and 18 μM in females. No difference in CA inhibition was observed between males and females.
- In the ongoing long term topical study with BID and TID 1% brinzolamide ophthalmic suspension, the rate of systemic drug absorption is much lower than oral 1 mg BID. Accumulation to concentrations of brinzolamide sufficient to saturate RBC CA II appears to require 6-9 months, and in some cases longer. Metabolite levels are lower at these months. Total inhibition appears to be leveling at approximately 40-70%, which is substantially less than that measured in oral study.

XI. Comments

(1) There is descripancy in lot number of the drug used in study C-92-34 on pages 6-0150 and 6-0163 of the NDA as AME-2497 and AME-2492, respectively. Please clarify the lot numbers of the drug used and also include batch and formulation IDs for all studies. There is incomplete information on the lot number of drug used in study C-95-47.

(2) The study report C-95-76 does not include data from the 12 week washout phase which was performed for the characterization of brinzolamide and N-desethyl brinzolamide elimination kinetics after the exit visit. Data is not available for the variance of the plasma and whole blood concentrations of brinzolamide and its metabolites, hence a confidence interval width, and power of the treatment comparison has not been stated by the sponsor. Serum creatinine results have not been reported yet. These results need to be submitted as soon as they are available.

(3) Patient #109 dropped the trial due to lid edema and contact dermatitis. The agency would like to know whether the patient was tested with the three different substances used in the study, singly, and in combination, according to the protocol C-92-34 (amendment 1 and 2). There are no indications of the details of the protocol study design being followed. We do note that a follow up was done on August 28, 31 and September 4, 1992 and patch test rechallenge was done from 10-7-92 to 10-12-92 and ocular rechallenge from 10-22-92 to 11-5-92, but it is not clear whether it was done in accordance to the amended protocol.

(4) For future submissions, the analytical validation for the assay procedures should be performed at the same time as that of the clinical study and should include reports for the entire study period. The validation for the determination of drug and metabolites in the whole blood was performed in Jan 1996 and that in plasma was performed in April/May 1996. The trial indicates a period from February to August 1996. Moreover, no information about the actual dates of study C-95-47 has been reported. This leads the agency to wonder whether the validation of the assay for determining the concentration of the drug is whole blood was performed at the time of the study.

(5) Looking at the whole blood concentration data for individual patients in study C-92-34, it can be seen that the blood levels are usually lower for patients with brown iris

as compared to blue eyes. Similarly, patients with brown eyes seemed to have a lower drop in IOP than those with blue eyes. Analysis of iris color comparison would be worth incorporating in future NDAs. Such differences are of concern in topical dosing due to the potential of melanin binding.

(6) For future study design, collection of urine data will be more helpful for information on drugs elimination kinetics and should be included in the protocol.

/S/ 5/22/97

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Peer Reviewer: E. Dennis Bashaw, Pharm. D. 6/3/97

CC: NDA 20816, ORIG
HFD-550/Div File
HFD-550/CSO/Lobianaco
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-870(attn:CDR.B.Murphy)
HFD-344(Viswanathan)

AE

APPEARS THIS WAY
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Appendix I- Studies

Study #	Short Summary Title
Topical Ophthalmic studies	
C-92-34	Multiple dose study of 3% brinzolamide ophthalmic suspension in normal male volunteers for 14 days
C-95-47	Multiple dose long term study (18 months) of 1% brinzolamide ophthalmic suspension in patients
Oral Studies	
C-95-76	Multiple dose study of 1 mg capsules of brizolamide in normal volunteers for 32 weeks
In Vitro Plasma Protein Binding Studies	

APPEARS THIS WAY
ON ORIGINAL

The assay has been well validated and is reproducible. For details see Summary (Section VIA).

DATA ANALYSIS: The concentration (μg/mL) of AL-4862 in whole blood at days 8, 15, 25-29, 43-49, 57 and 71 were calculated. The Cmax on day 8 and 15 and AUC(0-∞), -ke, T1/2 have been calculated. There were two drop outs from the study. For details see summary (section VII).

SAFETY ASSESMENT: Adverse events were defined as changes from baseline and were categorized as ocular and nonocular events related to therapy, ocular and nonocular events not related to therapy, serious events, nonserious events, hematology, blood chemistry, urinalysis, visual acuity, dilated fundus, cardiovascular data for pulse and mean arterial pressure.

MULTIPLE DOSE SHORT TERM SAFETY STUDY

PROTOCOL NO C-92-34 VOLUME 46 PAGE 6-0147

INVESTIGATOR AND LOCATION :

OBJECTIVE: Safety of topical AL-4862 3% ophthalmic suspension dosed TID in normal volunteers for 15 days.

FORMULATION: Drug Lot # AME-2497, the suspension was supplied open label in opaque, 5 mL volume, DROP-TAINERS® labeled with subject numbers.

STUDY DESIGN:
- Open-label, single group
- Dosing: AL-4862 3% dosed TID for 15 days
- Population: Normal Caucasian males aged 25-53
- Wash out phase: fast for 12 hours at the Before Baseline Exam and the Day 15 Exam
- Blood samples: day 8 and 15 (2 hours after last dose), semi-monthly blood level analysis done on weeks 4, 6, 8, and 10.
- Urine samples: 24 hour collection on Before Baseline Exam and Day 15 Exam
- IOP measurement: Day 1, 3, 8, 15

Volunteers were asked to fast for 12 hours prior to the screening (before baseline). Study day 1 should be no more than three days after baseline. Patient called for examination on study day 1, 3, 8 and 15. Dose to be administered to each eye 20-30 minutes after IOP measurements.

ASSAY:

MULTIPLE-DOSE LONG TERM STUDY

PROTOCOL NO C-95-47 VOLUME 47 PAGE 6-0525

INVESTIGATOR ANF LOCATION: multicenter (3),

OBJECTIVE: The objective of this study was to evaluate the IOP-lowering efficacy and long term safety following BID and TID administration of 1% AL-4862 compared to BID administration of 0.5% Timolol in patients with primary angle glaucoma or ocular hypertension.

FORMULATION: suspension, Drug Lot number not provided.

STUDY DESIGN: Triple-masked, parallel trial with three treatment groups.

Dosing: AL-4862 1% dosed BID
AL-4862 1% dosed TID
Timolol 0.5% dosed BID

Population: 15 Patients with primary open angle glaucoma

Washout phase: 5 days-3 weeks depending on medication used

Blood sampling: Baseline and prior to morning doses on months 3, 6, 9, 12 (ongoing study till 18 months)

ASSAY:

DATA ANALYSIS: The results were normalized for hematocrit to give RBC concentrations. RBC concentrations of AL-4862 and AL-8520, and total and CA II activities reported.

MULTIPLE DOSE ORAL STUDY

STUDY NO C-95-76 VOLUME 47 PAGE 6-0646

INVESTIGATOR AND LOCATION:

OBJECTIVE: To characterize the steady-state pharmacokinetics of Brinzolamide and metabolites and to assess steady-state carbonic anhydrase activity in red blood cells

FORMULATION: (Lot no APE-2798) capsules

STUDY DESIGN: Double-Masked, Parallel group, Placebo-Controlled, normal volunteers (6 males/7 females)

Dosing: BID for 32 weeks

Blood sampling: Prior to and 12 hours following first dose
Morning pre-dose samples then collected at bi-weekly intervals over the next 32 weeks

Plasma sampling: Prior to dosing, 0.5, 1, 2, 4, 8, 12 hours following the morning dose on Day 1, week 16 and week 32 exit visit.

Urine sampling: prior to dosing, over the 0-12 and 12-24 hour interval following the final dose

Clinical Pharmacology/Biopharmaceutics Review

NDA:	20-816	SUBMISSION DATE: 12/15/97
PRODUCT:	Brinzolamide Ophthalmic Suspension 1% AZOPT™	
SPONSOR:	Alcon Laboratories Ft. Worth, Tx.	REVIEWER: Veneeta Tandon, Ph.D.

MEMO

Recommendation

This submission is in response to the approvable letter sent to the sponsor on 12/4/97. The sponsor has adequately responded to the issues regarding the Human Pharmacokinetics section for this NDA, and the reviewer recommends approval from the pharmacokinetics standpoint.

Responses by the sponsor

One of the issues were regarding the discrepancy in the lot numbers used in study C-92-34 and C-95-47. The sponsor has given information regarding the correct lot numbers.

The second question was regarding the data for the 12 week washout phase for study report C-95-76. The sponsor has provided the data with the descriptive statistics. During the 12 week washout phase the mean whole blood concentration of brinzolamide fell from 25.10 ± 2.92 μM from the start of the washout phase (week 0) to 11.47 ± 1.79 μM at week 12. At week 12 of the washout phase the male subjects had a mean concentration of 12 ± 2.25 μM, where as females had a mean concentration of 11.02 ± 1.30 μM.

For the metabolite, N-desethyl brinzolamide the mean whole blood concentrations fell from 13.18 ± 7.85 μM at week 0 to 5.88 ± 3.18 μM at week 12 of the washout phase. The females showed a higher level of the metabolite at the end of the 12 week. It was 7.67 ± 3.37 μM for the females vs 3.79 ± 0.92 μM for the male subjects.

These results show that after oral administration of 1 mg of brinzolamide BID for 32 weeks, the drug as well as the major metabolite were detectable in the whole blood at the end of the 12 week washout phase, though there was a steady decline in the concentrations. Plasma concentrations were not measured during the 12 week washout. These results are satisfactory.

2/10/98

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Peer Reviewer: E. Dennis Bashaw, Pharm. D. Ed 2/10/96

CC: NDA 20816 (response to approvable letter)
HFD-550/Div File
HFD-550/CSO/Lobianaco
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-870(attn:CDR.B.Murphy)
HFD-344(Viswanathan)

APPEARS THIS WAY
ON ORIGINAL