CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20706

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Holmes
550

FEB -- 7 1997

Clinical Pharmacology/Biopharmaceutics Review

Emedastine Difumarate Ophthalmic Soln. 0.05%
NDA 20-706
EMADINE® 0.05%
Reviewer: E.D. Bashaw, Pharm.D.
APW

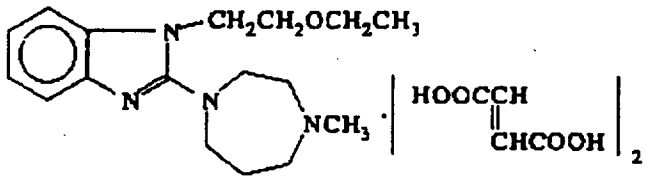
Alcon Laboratories
Ft. Worth, Tx. 76134

Submission Date:
March 27, 1996
April 3, 1996
Aug. 22, 1996

Review of an NDA

I. Background

Emedastine is a histamine-H_1 antagonist. It has been developed by Alcon Laboratories under this NDA as a topical solution for external application to the eye. The applicant (Alcon) is seeking approval for the relief of signs and symptoms of allergic conjunctivitis. Chemically it is 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl) benzimidazole. It has the following structure:



Emedastine was originally developed as an H_1-antagonist by and is marketed in as an orally administered anti-histamine under the tradename DAREN®. It is not marketed anywhere else in the world either as a topical or oral agent. There are no plans, at this time, to develop the oral formulation.

II. Recommendation

Based on the limited ophthalmic dosing data submitted in this study it appears that the in vivo absorption of drug following dosing with the 0.05% soln. will be minimal. In a study investigating the pharmacokinetics of emedastine, following topical ophthalmic BID steady-state dosing, less than 10% of the plasma samples on day 15 had quantifiable plasma levels (LQL=0.3ng/ml) and no plasma level was above 0.5ng/ml following dosing with the to-be-marketed 0.05% soln. These levels are approximately 10 fold lower than those seen following steady-state oral dosing with a 2mg dose. While the dosing regimen proposed for marketing (QID dosing) was not studied pharmacokinetically, it was studied clinically, and based on extrapolations of both the ophthalmic and oral dosing data it appears that the applicant has met the requirements for biopharmaceutic approval of the application.

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Appendix I-Ophthalmic Studies

III. Biopharmaceutic Study Overview

In support of the pharmacokinetic portion of this NDA the applicant has submitted the results of four in vivo pharmacokinetic studies using oral dosing and one study using ophthalmic dosing. Of the four oral dosing studies one used an experimental controlled release formulation, one was a food fasting study, one was a single dose BE study, and the other was a dose proportionality study. As neither the controlled release dosage form nor the effect of a high fat meal on bioavailability is relevant to the approval of this application, neither of these studies will be reviewed. The results of the other two oral dosing studies will be used in a supportive manner in confirmation of some of the ophthalmic data and the demonstration of linear pharmacokinetics following higher oral doses. The only so-called "pivotal" study contained in this application is the ophthalmic dosing study (C93-016).

IV. Analytical Methodology

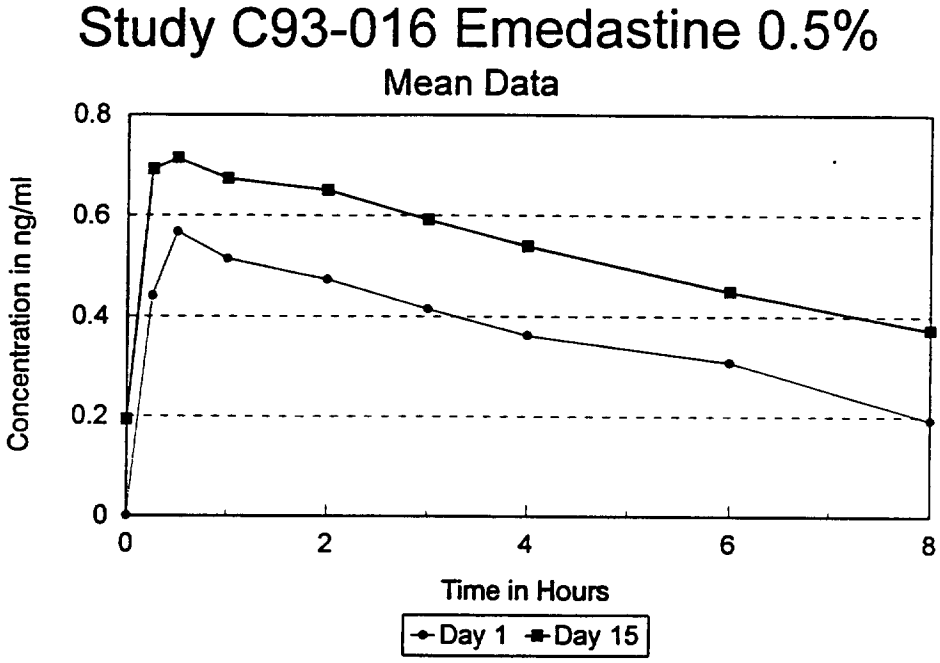
V. Ophthalmic Dosing

Study C93-016

As part of the development of the ophthalmic indication the applicant undertook dose proportionality study using range of doses following both single and multiple doses. A total of forty healthy subjects (male and female) were enrolled and randomized to one of the four treatment groups. The trial was designed as a parallel group study using four different treatment groups of 10 subjects each. Each subject was randomized to receive two drops of either a 0.5%, 0.1%, 0.05%, or a 0.01% solution of emedastine in each eye twice daily for fifteen days. On days 1 and 15 blood samples were collected for pharmacokinetic analysis. According to the pharmacokinetic plan provided by the sponsor, the resulting data was to have been analyzed for AUC, Cmax, Tmax, half-life and elimination rate. Attached as pages 2-8 in Appendix I are the associated raw data tables and study summary sheet for this trial.

Results

As noted above in the analytical section, out of a total of 693 samples analyzed only 25% of the samples (175/693) contained quantifiable levels of emedastine. Of these 175 samples, fully 70% (125/175) of them came from the 0.5% treatment leg. The remaining treatments had sporadic plasma levels in only a few individuals and the data was not suitable for pharmacokinetic analysis. A graphical representation of the mean data from the 0.5% treatment leg is presented below:



From the data collected in this treatment group the following pharmacokinetic parameters were calculated.

	AUC_{0-8}(ng*hr/ml)	Cmax(ng/ml)	Tmax(hr.)	T1/2(hrs.)
Day 1	3.46+/-1.46	0.64+/-0.19	0.67+/-0.25	9.4+/-2.7
Day 15	5.31+/-1.41	0.94+/-0.33	0.75+/-0.58	10.2+/-4.1
Ratio Day 15:1	1.53	1.47	-	-

The data indicates that, following topical ocular dosing, emedastine has a half-life of approximately 10hrs. and the degree of accumulation seen from day 1 to 15 is consistent with this half-life. While it is impossible to determine the bioavailability of emedastine from this study, the fact that plasma levels peak at approximately 3/4 of an hour indicates that whatever amount is absorbed is absorbed relatively rapidly.

One of the limitations of this trial is that the dosing regimen for marketing is two drops in each eye every six hours, not every 12 hours as done in this study. The reason for not doing a proper study with q6hr dosing is unknown. The applicant contends that such a study is unnecessary as the safety of emedastine at higher oral doses has already been shown in other

trials and as emedastine has linear pharmacokinetics at these higher doses, that one could extrapolate the expected plasma levels from the 0.5% data.

Discussion

The argument put forth by the sponsor is as follows. Assuming the pharmacokinetics of emedastine are linear (see oral dosing study section below), one can determine the degree of accumulation based on q6hr dosing using the standard equation for accumulation, where:

$$R = \frac{1}{1-e^{-k\tau}}$$

R= Accumulation Ratio

k=Terminal elimination rate

τ= Dosing interval

If the observed half-life is 10hrs. and the dosing interval is 6hrs then the accumulation ratio would be 2.93, or to put it another way, stead-state levels would be 2.93 times those following a single dose. Assuming linear pharmacokinetics, the observed peak concentration following a single dose of 0.5% emedastine was 0.64ng/ml. As this strength represents a 10x increase over the proposed 0.05% strength, again assuming linear pharmacokinetics, one could estimate the expected peak concentration of the 0.05% product following a single dose to be 0.064ng/ml (below the limit of detection). If we then multiply the estimated peak plasma concentration by the calculated accumulation ratio of 2.93 one would get a predicted steady-state concentration of 0.19ng/ml, again below the limit of detection, and further evidence, according to the sponsor, of the safety and low bioavailability of emedastine.

While the calculation of an estimated peak plasma concentration is interesting, it overlooks a basic fact, that is that the applicant used the wrong dosing interval in their pharmacokinetic study. It is likely, but not confirmed in the package, that originally the applicant intended upon a q12hr dosing interval and that the q6hr interval was decided upon after the study was performed. Instead of performing a new study the applicant elected to extrapolate plasma concentrations based on the current study. Such a direct explanation would be preferable to the argument and calculations put forth here. The applicant's estimation of a peak plasma concentration at steady-state for emedastine 0.05% is based upon standard pharmcokinetic relationships and is supported by the observed data in the 0.05% treatment leg in that only 8% (15/180) of the samples had detectable levels of emedastine. Of these levels the highest single value at steady-state was 0.46ng/ml. While this represents a concentration almost 2x that predicted by the applicant, the fact that 92% of the samples are below the 0.3ng/ml LQL does tend to support their calculations and conclusions.

Conclusions

From this reviewer's standpoint the applicant has demonstrated the singularly low plasma levels produced by topical ophthalmic administration of the drug substance. Using the to-be-marketed concentration the sponsor could not reliably detect plasma levels of emedastine using a q12hr dosing interval to steady-state. The use of a q6hr dosing interval would cause

additional accumulation to occur, above that which was seen in this trial. Based on extrapolations from the 0.5% strength dosage form, the resulting peak plasma levels from the to-be-marketed concentration would still be below the limit of detection (0.5ng/ml). While this type of extrapolation is not the preferred way of evaluating the pharmacokinetics of any drug, in this instance, where the probability of detecting drug is low and where there is data from higher doses, it is acceptable.

VI. Oral Dosing

As noted earlier in the overview section of this review there were a total of four oral dosing studies submitted as part of this review. Of them, Kanebo-1 and Kanebo-4 were selected for inclusion into this review package. Unfortunately neither of these studies was well documented. No analytical validation data was submitted, no raw pharmacokinetic data was provided and no detailed assessment of the results were provided. Instead, a translation of the study summary report was provided from the original Japanese. This translated document is the only link provided by the sponsor to the original source data which must still reside in Japan. Even with these limitations some useful information can be extracted from the study reports. The results in and of themselves cannot be accepted as definitive in nature and without the mutual support of the validated ophthalmic dosing study, these studies would not be acceptable (see Comment #1).

Kanebo-1

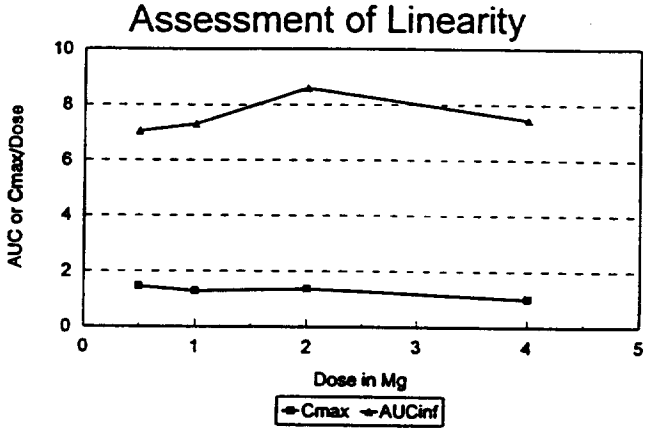
This study was a phase I, single and multiple dose, dose escalation study in healthy Japanese males. During the first part of this study five males between the ages of 27 and 40 received single oral doses of 0.5, 1, 2, and 4mg of emedastine difumarate following a meal. The exact content of the meal was undisclosed. The doses were separated by a 1 week washout period between the 0.5, 1, and 2mg doses and by a 7week washout period between the 2 and 4mg doses. The 2mg dosage leg was performed twice, once with a meal and once fasted. Both plasma and urine were collected according to the following schedule: blood: Pre-dose, and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours after dosing ,urine:0-3, 3-6, 6-9, 9-12, 12-24 hours after dosing.

As noted above the applicant did not provide the raw data from this trial to the Agency for review (according to the applicant it was unavailable). Reproduced below are the tabular results of the trial provided in the study report.

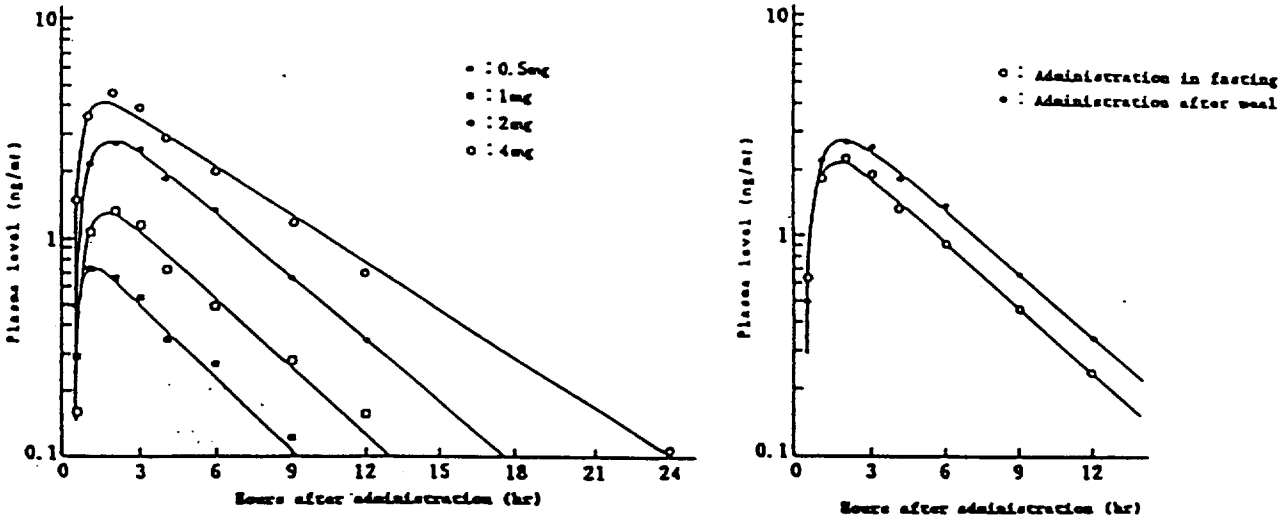
Dose (mg)	V/F (l)	ka (hr^{-1})	kel (hr^{-1})	t_{lag} (hr)	C_{max} (ng/ml)	t_{max} (hr)	t½ (hr)	MRT (hr)	VRT (hr^2)	$AUC_{0-\infty}$ (ng·hr/ml)
0.5	319.4 ±25.9	4.02 ±1.72	0.251 ±0.036	0.402 ±0.042	0.736 ±0.063	1.14 ±0.06	2.76 ±0.39	4.23 ±0.57	15.9 ± 4.5	3.52 ±0.58
1	330.8 ±84.8	2.11 ±1.51	0.234 ±0.086	0.453 ±0.046	1.30 ± 0.36	1.63 ±0.13	2.96 ±1.09	4.75 ±1.61	18.5 ± 13.4	7.31 ±3.27
2	300.9 ±12.6	1.65 ±0.21	0.219 ±0.008	0.412 ±0.012	2.76 ± 0.12	1.83 ±0.02	3.16 ±0.12	5.17 ±0.19	21.2 ± 1.5	17.2 ± 1.0
4	451.9 ±25.9	2.40 ±0.78	0.168 ±0.006	0.354 ±0.051	4.10 ± 0.24	1.54 ±0.06	4.12 ±0.15	6.36 ±0.26	35.5 ± 2.6	29.8 ± 2.0

Mean ± (n = 5), S.D. indicates interpolating error in interpolation

The primary use of this data, since oral dosing is not an issue with this product, is the demonstration of dose linearity following oral dosing. The following figure is a graphical representation of the degree of linearity present in the data.

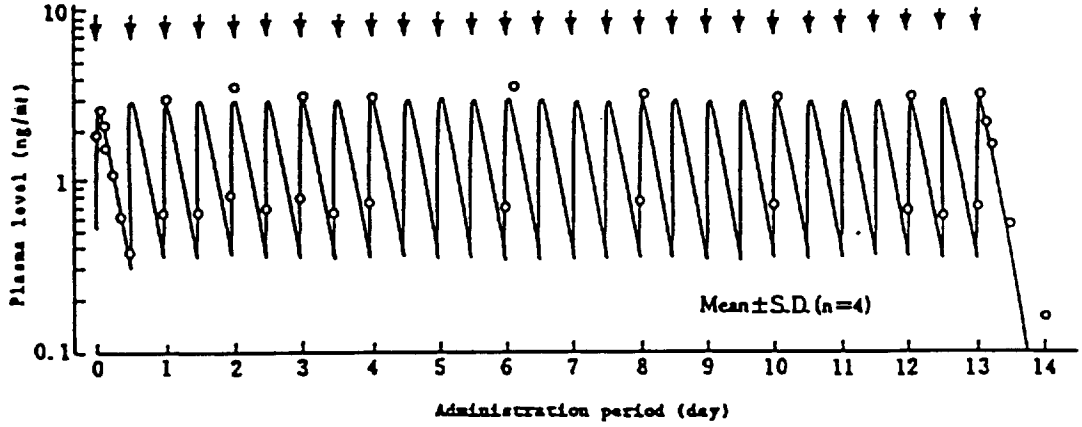


Ideally, under the conditions of this graph, a linear system would reveal itself by producing lines with a slope of zero across the range of tested doses. While minor fluctuations are seen in the data here, these are most likely due to the very small N used (5) and the data can be said to be indicative of linear pharmacokinetics. This is also borne out by a plot of the mean data from each treatment as shown below:



As presented above it is clear that emedastine demonstrated linear pharmacokinetics over the range of 0.5 to 4mg following oral dosing. It is also clear that food has an impact on the oral absorption of emedastine. As current plans for emedastine do not include oral dosing, further research into the food effect is not warranted at this time. Should emedastine later be developed as an oral compound, further research in this area using a controlled diet will be necessary.

As part of the second phase of this study, an additional group of five healthy Japanese subjects were enrolled in the trial and received 2mg of emedastine twice daily for 14 days. The graphical results of this trial are reproduced below, no tabular data was provided by the sponsor.



The results of this phase of the trial suggest, that the dosing of emedastine on a q12hr schedule results in minimal accumulation of drug. This finding is consistent with the observed 3-4hr half-life found after a single dose of emedastine.

As for the urinary data collected during this study, the urine samples were analyzed for intact emedastine and metabolites. Only about 5% of the administered dose was recovered in the urine unchanged. An additional 37% of the dose was recovered as metabolites. Reproduced below is a proposed metabolic scheme based on the urinary data.

While the data extracted from this trial is useful the lack of assay validation, raw data, and a detailed analysis makes the use of this data limited. Its inclusion in this review is only intended to support the existence of linear pharmacokinetics following higher oral dosing. While still suspect, as there is no supporting raw data, the data does demonstrate a pattern consistent with linear pharmacokinetics. Normally, it would be possible to extract more information from this trial and make more definitive statements on the disposition of emedastine from this data, but without the validation and raw data such speculation would remain only that.

Kanebo-4

This trial, like Kanebo-1, was a trial done by the original Japanese developer of this product. It suffers from a similar lack of detail as the previous study did. It is being included in this review only because it is a single dose bioequivalency study in 16 subjects. This increase in N from the previous study is the driving reason for inclusion. The question that this study was primarily designed to answer, namely bioequivalency between the 1mg experimental capsule and a to-be-marketed 2mg capsule, is not relevant to the approval of the ophthalmic solution and will not be addressed in any detail.

Briefly a series of 16 healthy Japanese subjects were enrolled in this trial and were divided into two groups of 8. Each group received either 2x1mg capsules or 1x2mg capsule following a 10 hr. fast. Plasma samples were collected at pre-dose and 1, 2, 3, 4, 6, 9, 12, and 24 hours after dosing. Following a seven day washout period each treatment group returned to the study unit and were crossed over to the other treatment.

Unlike the previous study the applicant was able to provide the raw data from this trial and an analysis of it. Unfortunately the analysis provided by the sponsor did not include half-life. Using the raw data from this trial, this reviewer undertook an additional analysis of the raw data using WinNONLIN v1.0. Using both the 1 and 2 compartment extravascular models the data was fit. Examination of the data indicated that the 1 compartment model was the proper model and an estimate of k of $0.15hr^{-1}$, equal to a half-life of ~4.6hrs was obtained. This half-life estimate agrees well the observed half-life for emadastine from the previous oral dosing study. This estimate of half-life coming from a suitably large dataset (16 subjects) tends to validate the applicant's position that any accumulation with repeated topical ophthalmic dosing would be minimal.

Even though the data from both of the oral dosing studies was unvalidated and cannot be considered pivotal, both studies have provided important supportive evidence for emedastine. Both the demonstration of linear plasma kinetics with oral dosing and the determination of a half-life for emedastine are important in supporting the applicants view that extrapolation from q12hr dosing data to q6hr data is not problematic.

VII. Protein Binding

In the pharmacokinetic summary provided to this reviewer the sponsor indicates that two protein binding studies were performed using emedastine. These studies indicated that emedastine was 65% bound to plasma proteins at a concentration of 30ng/ml, greatly in excess of the plasma levels observed following ophthalmic dosing. In addition the primary binding protein

was identified as α_1-acid glycoprotein. Unfortunately neither study report nor journal article was submitted in this application in support of these claims. Since this is an ophthalmic product and the observed plasma levels are generally below the limit of detection, no action is indicated at this time. The sponsor will be informed (Comment #2) that they should pay more attention when they cite materials in the summaries that the material is actually provided for review.

VIII. Conclusions

In this NDA the applicant has provided data on the observed plasma concentrations of emedastine following repeated dosing with their topical ophthalmic product. At the to-be-marketed strength, using a q12hr dosing interval, few plasma concentrations <10% were above the limit of detection. Extrapolation using the results of higher topical ophthalmic doses, indicates that if a q6hr dosing interval was used the majority of the plasma concentrations would still be at the limit of detection. Using unvalidated oral dosing data the applicant has submitted supportive data of the linearity of emedastine at single oral doses of 0.5-4mg and multiple doses of 2mg. Additional unvalidated oral dosing data has also been used by the sponsor to demonstrate the reliability of an estimate of plasma half-life of 4.6hrs which is critical for the calculation of accumulation of emedastine in plasma. While a much longer half-life is reported for ophthalmic dosing (~11 hrs.), no explanation for this discrepency has been made by this sponsor. A possible explanation for this may be the presence of a genetic difference between the Japanese subjects in the Kanebo trials and the primarily caucasian population used in the ophthalmic study. As it is the 11hr. half-life for the ophthalmic dosing is in keeping with the degree of accumulation seen in the ophthalmic trial. The applicant should be asked to address this issue as part of their analytical response for the Kanebo trials.

While not normally a common practice, the acceptance of the use of unvalidated oral dosing data-for limited objectives, is acceptable here due to the lack of ophthalmic plasma levels at clincial doses. By limiting the use of this data to the demonstration of linearity one is attempting to use the data without depending upon it exclusively for approval.

Taken as a whole it appears that the applicant has adequately addressed the in vivo pharmacokinetic requirements for approval. The sponsor should, however, address the issues outlined below in Comments #1 and 3.

IX. Comments

1. In this application the applicant has relied upon some of the pharmacokinetic information originally developed by Kanebo Pharm. of Japan. The reports provided are inadequate for use as pivotal data as no analytical validation information is provided for the assay technique used. In addition, the majority of the Kanebo reports lack raw data or an explanation of the data analysis conducted on the data. While in this NDA these oversights were not critical, the applicant should take note that in future NDA's the approvability of their product could easily hinge on these types of data.

2. In the pharmacokinetic summary of this application the applicant discusses the results of in vitro plasma protein binding studies that are not contained in this NDA. The applicant cannot cite or use data that is not contained in their NDA. While the low levels of drug present in the plasma with emedastine are unlikely to cause any protein binding interactions, the failure of the applicant to include information cited in their own narrative is glaring.

3. As part of the data supplied with the Kanebo trials are results indicating a 4 hr. half-life for emedastine. This does not agree with the 11 hr. half-life reported for emedastine in the ophthalmic dosing trial. The applicant needs to address this issue as part of their analytical response.

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

J.A. LAZUR

Secondary Review, ~~Nick Fleischer, Ph.D.~~ 2/7/97

CC: NDA 20-706 (ORIG),
HFD-550/DIV File
HFD-550/CSO/Holmes
HFD-880(Bashaw)
HFD-880(Fleischer) M.I
HFD-~~870~~ 870 (~~Clarence Bott, Drug, Chron Files~~)
HFD-344(Viswanathan)

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Appendix I-Ophthalmic Studies

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NDA/IND# 20-706 Suppl/Amend.# ORIG Submission Date: 3/27/96 Volume: 1.13

Study Type: Ophthalmic Dosing Study # C93-016

Study Title: Safety Evaluation and Plasma Concentrations of Topical Emedastine in Healthy Volunteers

Clinical Investigator	Analytical Investigator: Beth A. McCue, MS
Site	Site: Alcon Laboratories
	Bioanalytical Dept.
	Fort Worth, TX 76104

Single Dose: Y Multiple Dose: Y Washout Period: NONE

Cross-Over N Parallel Y Other Design:

Fasted n.a. Food Study FDA High Fat Breakfast

If fasted, how long (hrs.)?

Subject Breakdown

Normal Y Patients Young Y Elderly Renal Hepatic

	Subject Type		Female	Group	0.50%	N=	10	M=	4	F=	6
Weight	Mean	unk	Range unk	Group	0.10%	N=	10	M=	3	F=	7
Age	Mean	36.5	Range 18-49yrs. old	Group	0.05%	N=	10	M=	5	F=	5
	Subject Type		Male	Group	0.01%	N=	10	M=	5	F=	5
Weight	Mean	unk	Range unk	Group		N=		M=		F=	
Age	Mean	28.5	Range 18-56yrs. old	Group		N=		M=		F=	

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
A	2 drops in each eye every 12 hours for 15 days	Eye Drops	0.50%	AOE-2618	UNKNOWN
B		Eye Drops	0.10%	AOE-2617	UNKNOWN
C		Eye Drops	0.05%	AOE-2616	UNKNOWN
D		Eye Drops	0.01%	AOE-2615	UNKNOWN

Sampling Times

Plasma Day 1 and 15, Prior to dosing and at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dosing.

Urine N/A

Feces N/A

Assay Method:

Assay Sensitivity

Assay Accuracy

Labeling Claims From Study: There is low systemic exposure to emedastine following BID topical ocular dosing of concentrations up to 0.5%. Using the to-be-marketed 0.05% concentration, plasma levels of emedastine are essentially undetectable.

Table 1

Emedastine Plasma Concentrations for the 0.5% Dose Group - Protocol C-93-16

Day	Time (Hours)	Subject 201	205	209	213	220	222	226	230	234	239
1	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										
15	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										

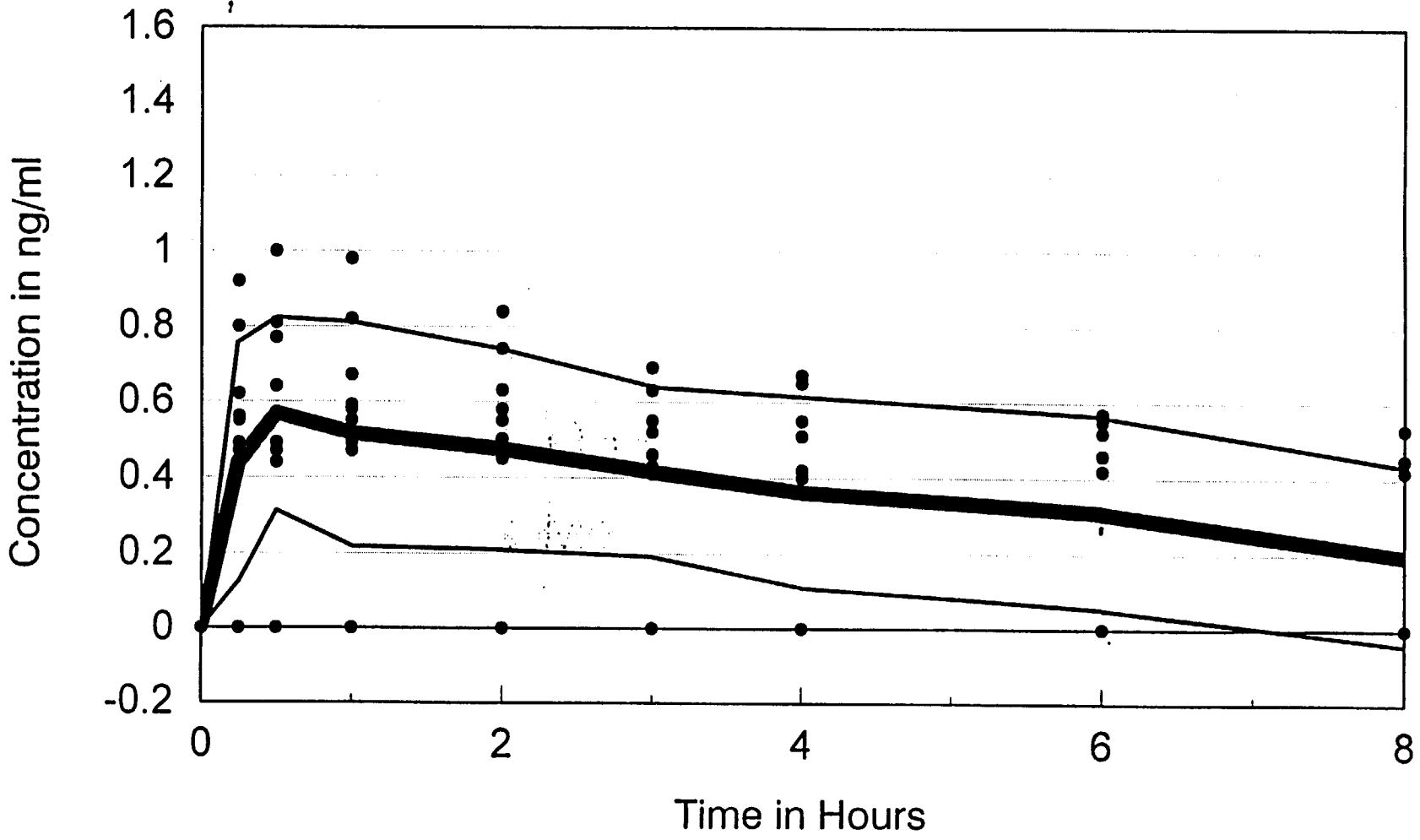
NA = Not assayed. NS = No Sample Collected.

BLQ = Below Limit of Quantitation (<0.3 ng/mL)

* = Serum sample received for this time point.

Study C93-016 Emedastine 0.5%

Single Dose-Mean Data +/- 1STD. DEV.



Study C93-016 Emedastine 0.5%

Multiple Dose-Mean Data +/- 1STD. DEV.

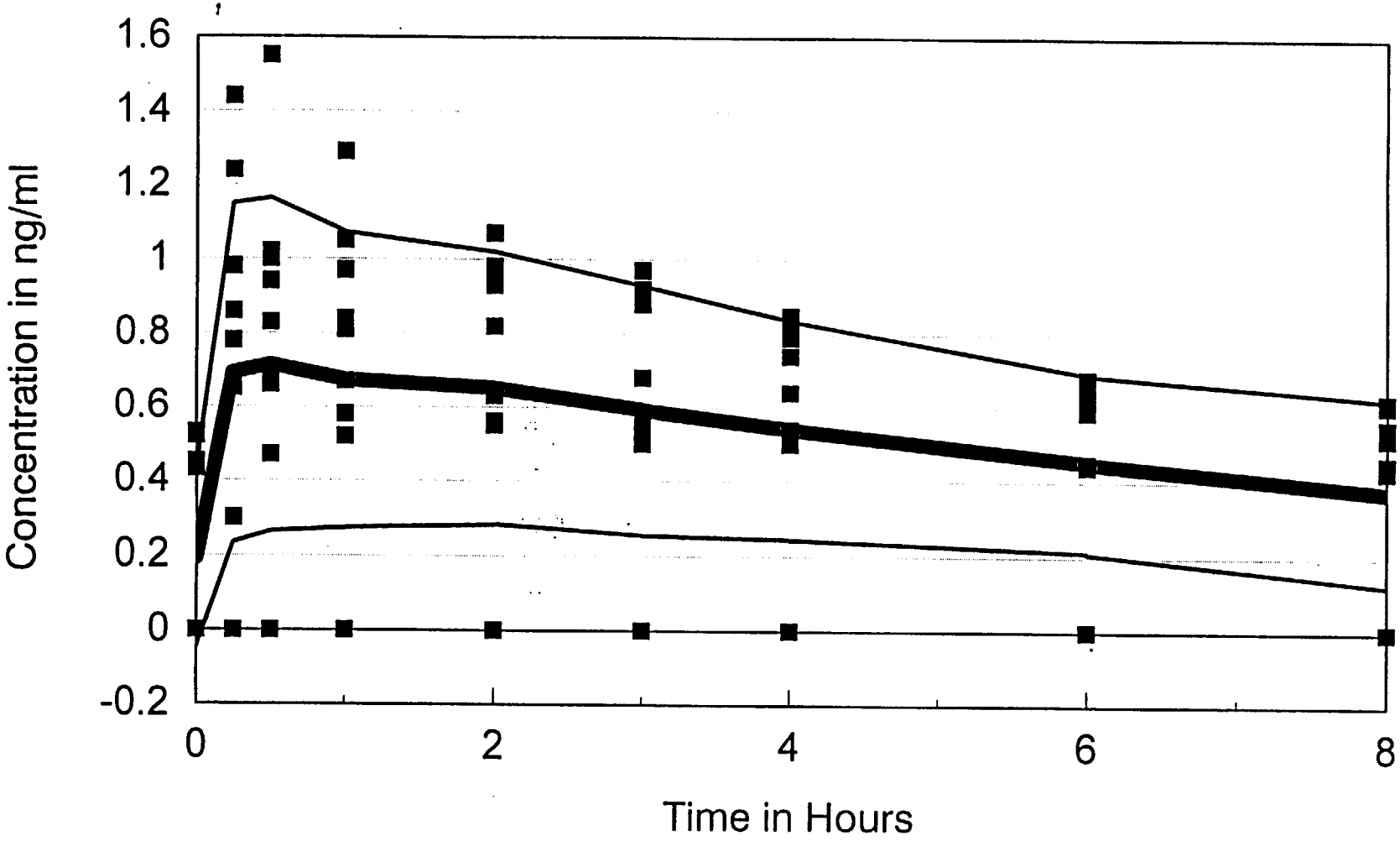


Table 2

Emedastine Plasma Concentrations for the 0.1% Dose Group - Protocol C-93-16

Day	Time (Hours)	Subject 204	208	210	215	218	223	228	229	233	240
1	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										
15	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										

Quantifiable values in bold for emphasis.

BLQ = Below Limit of Quantitation (<0.3 ng/mL)

* = Serum sample received for this time point.

Table 3

Emedastine Plasma Concentrations for the 0.05% Dose Group - Protocol C-93-16

Day	Time (Hours)	Subject 202	206	211	214	217	221	227	232	235	238
1	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										
15	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										

Quantifiable values in bold for emphasis.

BLQ = Below Limit of Quantitation (<0.3 ng/mL)

* = Serum sample received for this time point.

Table 4

Emedastine Plasma Concentrations for the 0.01% Dose Group - Protocol C-93-16

Day	Time (Hours)	Subject 203	207	212	216	219	224	225	231	236	237
1	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										
15	Predose										
	0.25										
	0.5										
	1										
	2										
	3										
	4										
	6										
	8										

Quantifiable values in bold for emphasis.

BLQ = Below Limit of Quantitation (<0.3 ng/mL)

* = Serum sample received for this time point.

1 page

PURGED

DRAFT Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20706

ADMINISTRATIVE DOCUMENTS

PART 15. DEBARMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal, Food, Drug and Cosmetic Act, Alcon Laboratories, Inc., certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity in connection with this application, the services of any person listed pursuant to Section 306(e) as debarred under Subsections 306(a) or (b) of the Act.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-706 Supplement # NA Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 550 Trade (generic) name/dosage form: Emadine (emedastine difumarate ophthalmic solution) 0.05% Action: (AP) AE NA

Applicant Alcon Labs Therapeutic Class 15

Indication(s) previously approved NA

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application temporary relief of the signs and symptoms of allergic conjunctivitis

(For supplements, answer the following questions in relation to the proposed indication.)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Joanne M Holmes, PhClinical Reviewer — 12/11/97

Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig NDA/PLA # 20-706
HFD 550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

PART 13. PATENT AND EXCLUSIVITY INFORMATION

A. Patents - Information on all patents that claim the drug or method of using the drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug.

Patent Number	Owner	Claim Type	Expiration Date
U.S.4,430,343	Kanebo, Ltd.	Drug substance and Method of use	10/22/02
U.S. 5,441,958	Alcon Laboratories, Inc.	Method of use	12/08/13

B. Exclusivity - Request for Five Year Exclusivity

The applicant requests a five year period of market exclusivity based on the following information:

1. Emedastine difumarate, the active ingredient, is a new chemical entity.
2. No NDA under Section 505 of the Act has previously been approved by the FDA containing emedastine as the active moiety.
3. This application is the pioneer NDA for emedastine difumarate.

US005441958A

United States Patent [19]

Yanni et al.

[11] Patent Number: 5,441,958

[45] Date of Patent: Aug. 15, 1995

[54] **OPHTHALMIC COMPOSITIONS COMPRISING EMEDASTINE AND METHODS FOR THEIR USE**

[75] Inventors: **John M. Yanni**, Burleson; **Stella M. Robertson**, Arlington, both of Tex.; **Shigetoshi Okumura**; Hitoshi Tanaka, both of Nara, Japan; Tadayuki Saito, Osaka, Japan

[73] Assignee: **Alcon Laboratories, Inc.**, Fort. Worth, Tex.

[21] Appl. No.: 163,973

[22] Filed: Dec. 8, 1993

[30] **Foreign Application Priority Data**

Dec. 9, 1992 [JP] Japan 4-329216

[51] **Int. Cl.**[6] **A61K 31/50**

[52] **U.S. Cl.** **514/253**; 514/912

[58] **Field of Search** 514/253, 912

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,430,343	2/1984	Iemura et al.	424/250
5,192,780	3/1993	York et al.	514/357

OTHER PUBLICATIONS

Miller, J. et al., "Antazoline phosphate and naphazoline hydrochloride, singly and in combination for the treatment of allergic conjunctivitis–a controlled, double–blind clinical trial," *Ann. Allergy.*, 35:81–86 (1975).

Vandewalker, M. L., et al., "Efficacy of Vasocon–A and its components with conjunctival provaction testing (CPT)," *J. Allergy Clin. Immunol.*, 83:302 (1989).

Abelson, M. B., et al., "Effects of topically applied ocular decongestant and antihistamine," *Am. J. Ophthalmol.*, 90:254–257 (1980).

DeChant, K. L. and K. L. Goa, "Levocabastine. A Review of its pharmaceutical properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis," *Drugs*, 41:202–224 (1991).

Berdy et al., "Allergic conjunctivitis: A survey of new antihistamines," *J. Ocular Pharmacol.*, 7:313–324 (1991).

Yanni et al., "Effect of Lodoxamide on in vitro and in vivo conjunctival immediate hypersensitivity responses in rats," *Int. Arch. Allergy Immunol.*, 101:102–106 (1993).

Dunnett, C. W., "A multiple comparison procedure for comparing treatments with a control," *J. Am. Stat. Assoc.*, 50:1096–1121 (1955).

Bliss, C. and E. Gjorgy, *Vitamin Methods*, vol. 2, pp. 445–610, Academic Press, Inc. New York (1951).

Primary Examiner—Zohreh Fay

Attorney, Agent, or Firm—Sally Yeager

[57] **ABSTRACT**

Topical ophthalmic compositions comprising 1-(2-ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)-benzimidazole and its ophthalmically acceptable acid addition salts have been found to be useful in treating allergic conjunctivitis and related ailments.

5 Claims, No Drawings

United States Patent [19]

Iemura et al.

[11] **4,430,343**

[45] **Feb. 7, 1984**

[54] BENZIMIDAZOLE DERIVATIVES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

[75] Inventors: **Ryuichi Iemura**, Kawanisi; **Tsuneo Kawashima**, Kobe; **Toshikazu Fukuda**, Osaka; **Keizo Ito**, Osaka; **Takashi Nose**, Nara; **Goro Tsukamoto**, Toyonaka, all of Japan

[73] Assignee: **Kanebo, Ltd.**, Tokyo, Japan

[21] Appl. No.: 436,032

[22] Filed: Oct. 22, 1982

[30] **Foreign Application Priority Data**

Nov. 6, 1981 [JP] Japan 56-178804

[51] Int. Cl.³ A61K 31/495; A61K 31/55; C07D 403/02

[52] U.S. Cl. ..... 424/250; 424/273 R; 260/245.6; 544/370

[58] Field of Search ..... 544/370; 260/245.6; 424/250, 273 B

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,689,853	9/1954	Schenck et al.	260/309.2
3,423,413	1/1969	Priewe et al.	260/268
4,093,726	6/1978	Winn et al.	424/250

FOREIGN PATENT DOCUMENTS

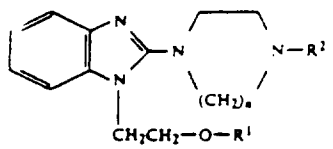
50-126682	10/1975	Japan	544/370

Primary Examiner—Alton D. Rollins

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

Novel benzimidazole derivatives of the formula:



(I)

wherein R^1 is an alkyl group having 1 to 3 carbon atoms, allyl group, propargyl group, or phenyl group; R^2 is hydrogen atom or an alkyl group having 1 to 3 carbon atoms; and n is 2 or 3, or pharmaceutically acceptable acid addition salts thereof, which have excellent antihistaminic activities and are useful as antiallergics for various allergic diseases, and a process for the preparation thereof, and an antihistaminic composition containing the compound as an active ingredient.

10 Claims, No Drawings

EXCLUSIVITY SUMMARY for NDA # 20-706 SUPPL # NA

Trade Name Emadine Generic Name emedastine difumarate ophthalmic solution, 0.05%

Applicant Name Alcon Labs HFD-550

Approval Date 12/29/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95

cc: Original NDA Division File HFD-[illegible] Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of [illegible] about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO **DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study #

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

_____
Signature
Title: Joanne Holmes, Proj Mgr

12/15/96
Date

_____
Signature of Division Director

12/31/96
Date

cc: Original NDA Division File HFD-~~85~~ 92 Mary Ann Holovac