PATENT AND EXCLUSIVITY INFORMATION

A. Below are listed all patents known to the applicant that claim the drug or a method of using the drug 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, sale, or use of the drug.

U.S. Patent No.:	4,911,920
Expiration Date:	March 27, 2007
Patent Owner:	Alcon Laboratories, Inc.
Claims for:	Drug Product (Composition/Formulation); Method of Use (Method for controlling and lowering intraocular pressure)

U.S. Patent No.:	5,540,918
Expiration Date:	July 30, 2013
Patent Owner:	Alcon Laboratories, Inc.
Claims for:	Drug Product (Composition/Formulation)

U.S. Patent No.:	4,342,783
Expiration Date:	June 30, 2000
Patent Owner:	Synthélabo
Claims for:	Drug Product (Composition/Formulation); Method of Use (Method for treating glaucoma)

U.S. Patent No.:	4,252,984
Expiration Date:	August 30, 1999
Patent Owner:	Synthélabo
Claims for:	Drug Substance (Active Ingredient)

B. Original Declaration for Patent Nos. 4,911,920, 5,540,918; 4,342,783; 4,252,984

The undersigned declares that U.S. Patent Nos. 4,911,920, 5,540,918; 4,342,783; and 4,252,984 cover the composition, formulation, and method of use of Levobetaxolol Hydrochloride Ophthalmic Suspension, 0.5%

Sally S. Yerger
Assistant General Counsel
(817) 551-4031

May 14 '99
Date

ITEM 14. 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.

Table 1

Patent Information That Claim the Drug on Method of Using the Drug

PATENT NUMBER	OWNER	CLAIM TYPE	EXPIRATION DATE
U.S. 4,911,920	Alcon Laboratories, Inc.	Drug Product (composition/formulation); Method of Use (method of controlling and lowering intraocular pressure)	03/27/2007
U.S. 5,540,918	Alcon Laboratories, Inc.	Drug Product (composition/formulation)	07/30/2013
U.S. 4,342,783	Synthelabo	Drug Product (composition/formulation); Method of Use (method for treating glaucoma)	06/30/2000
U.S. 4,252,984	Synthelabo	Drug Substance (Active Ingredient)	8/30/99

B. Exclusivity – Request for Five Year Exclusivity

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

1. Levobetaxolol hydrochloride, 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 levobetaxolol hydrochloride as the active moiety.
3. This application is the pioneer NDA for levobetaxolol hydrochloride.

United States Patent [19]

Jani et al.

[11] Patent Number: 4,911,920

[45] Date of Patent: Mar. 27, 1990

[54] SUSTAINED RELEASE, COMFORT FORMULATION FOR GLAUCOMA THERAPY

[75] Inventors: Rajni Jani; Robert G. Harris, both of Fort Worth, Tex.

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

[21] Appl. No.: 154,514

[22] Filed: Feb. 5, 1988

Related U.S. Application Data

[63] Continuation of Ser. No. 890,519, Jul. 30, 1986, abandoned, which is a continuation of Ser. No. 667,003, Oct. 31, 1984, abandoned.

[51] Int. Cl.[4] A61K 31/78

[52] U.S. Cl. 424/78; 424/81; 514/913

[58] Field of Search 514/913; 424/19, 78, 424/81

[56] References Cited

U.S. PATENT DOCUMENTS

3,867,519	2/1975	Michaels	424/19
3,962,414	6/1976	Michaels	424/19
3,987,163	10/1976	Rankin	424/78
4,127,674	11/1978	Leopold	424/324
4,207,890	6/1980	Mamajek et al	128/223
4,271,143	6/1981	Schoenwald et al.	424/78
4,407,792	10/1983	Schoenwald et al.	424/81
4,462,982	7/1984	Samejima et al.	429/19
4,521,414	6/1985	Chion et al.	514/229

OTHER PUBLICATIONS

Chem. Abst. 98:210936j (1983) Heath et al.

Primary Examiner—Shep K. Rose
Assistant Examiner—Zohreh A. Fay
Attorney, Agent, or Firm—James A. Arno; Gregg C. Brown; Sally Yeager

[57] ABSTRACT

Disclosed are nonstinging, sustained release ophthalmic formulations to control intraocular pressure in anti-glaucoma therapy comprising a basic active, a cation exchange resin, and, inter alia, an acidic mucommetic polymer. Also disclosed are methods of treatment comprising administering such formulations topically to the eye when indicated for control and lowering of intraocular pressure.

12 Claims, No Drawings

US005540918A

United States Patent [19]

Castillo et al.

[11] Patent Number: 5,540,918

[45] Date of Patent: Jul. 30, 1996

[54] **USE OF CERTAIN ANIONIC SURFACTANTS TO ENHANCE ANTIMICROBIAL EFFECTIVENESS OF OPHTHALMIC COMPOSITIONS**

[75] Inventors: **Ernesto J. Castillo**, Arlington; **Yusuf Ali**, Fort Worth, both of Tex.

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

[21] Appl. No.: **472,446**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[60] Division of Ser. No. 106,459, Aug. 13, 1993, which is a continuation-in-part of Ser. No. 937,228, Aug. 28, 1992, abandoned.

[51] Int. Cl.[6] A61K 31/74

[52] U.S. Cl. 424/78.04; 514/912

[58] Field of Search 424/427, 428, 424/78.04; 514/912

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,275,503	9/1966	Mamen et al.	167/22
4,485,029	11/1984	Kato et al.	252/106
4,911,920	3/1990	Jani et al.	424/78.04

FOREIGN PATENT DOCUMENTS

0194097	10/1986	European Pat. Off. .
0243145A2	10/1987	European Pat. Off. .
0429732A1	6/1991	European Pat. Off. .

Primary Examiner—Carlos Azpuru

Attorney, Agent, or Firm—Julie J. L. Cheng; Patrick M. Ryan

[57] **ABSTRACT**

Certain anionic surfactants are used to enhance antimicrobial effectiveness in comfortable, sustained release ophthalmic compositions containing polyelectrolytes, such as carboxyvinyl polymers, polystyrene sulfonic acid polymers and cationic exchange resins, as well as at least one active ingredient.

10 Claims, No Drawings

United States Patent [19]

Morselli et al.

[11] **4,342,783**

[45] **Aug. 3, 1982**

[54] **ANTI-GLAUCOMA AGENT**

[75] Inventors: **Paolo L. Morselli**, Meudon Bellevue, France; **Louis De Santis, Jr.**; **Robert Adamiki**, both of Fort Worth, Tex.

[73] Assignee: **Synthelabo**, Paris, France

[21] Appl. No.: **164,223**

[22] Filed: **Jun. 30, 1980**

[51] Int. Cl.³ **A61K 31/135**

[52] U.S. Cl. **424/330**

[58] Field of Search 424/330, 260/501.17, 260/501.19, 570.7

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,674,840	7/1972	Grandstrom et al.	260/570.7 X
3,712,890	1/1973	Lee	260/570.7 X
3,723,476	3/1973	Nakanishi et al.	424/325
3,873,600	3/1975	Brandstrom et al.	260/570.7 X
3,876,802	4/1975	Brandstrom et al.	424/330
3,888,898	6/1975	Koppe et al.	260/570.7 X
3,937,834	2/1976	Hunger et al.	424/330
4,085,136	4/1978	Tucker	260/570.7 X
4,145,442	3/1979	Bernstorm et al.	424/330

FOREIGN PATENT DOCUMENTS

5062M	1/1968	France	260/570.7
7015123	2/1971	France	260/570.7
7105224	2/1974	France	260/570.7

Primary Examiner—Douglas W. Robinson

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

1-{4-[2-(Cyclopropylmethoxy)-ethyl]-phenoxy}-3-isopropylamino-propan-2-ol and its pharmaceutically acceptable salts, in the form of a racemate or optical isomer, are useful as topical anti-glaucoma agents.

3 Claims, No Drawings

United States Patent [19]

Manoury et al.

[11] 4,252,984

[45] Feb. 24, 1981

[54] **PHENOL ETHERS**

[75] Inventors: **Philippe M. J. Manoury, L'Hay les Roses; Icilio A. G. Cavero; Henry Najer, both of Paris; Don Pierre R. L. Giudicelli, Fontenay sous Bois, all of France**

[73] Assignee: **Synthelabo, Paris, France**

[21] Appl. No.: **734,359**

[22] Filed: **Oct. 20, 1976**

[30] **Foreign Application Priority Data**

Nov 6, 1975 [FR] France 75 33899

[51] Int. Cl.[1] **C07C 93/06**

[52] U.S. Cl. ..... **564/349**; 260/348.43; 260/348.63; 260/465 E; 260/501.17; 260/501.19; 424/316; 424/330; 564/223; 568/27; 568/28; 568/61; 568/67; 568/626; 568/630

[58] Field of Search 260/501.17, 501.19, 260/570.7; 424/316, 330

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,674,840	7/1972	Grandstrom et al.	260/570.7 X
3,712,890	1/1973	Lee	260/570.7 X
3,723,476	3/1973	Nakanishi et al.	260/570.7 X
3,873,600	3/1975	Brandstrom et al.	260/570.7 X
3,886,898	6/1975	Koppe et al.	260/570.7 X
4,085,136	4/1978	Tucker	260/570.7 X

FOREIGN PATENT DOCUMENTS

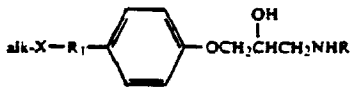
5662 M	1/1968	France	260/570.7
7015123	2/1971	France	260/570.7
7105224	2/1974	France	260/570.7

Primary Examiner—Robert V. Hines

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

The invention provides phenol ethers of the formula:



wherein

R is branched C_{3-4} alkyl, C_{3-4} cycloalkyl, branched cyano(C_{3-4} alkyl), phenyl(C_{2-3} alkyl), halophenyl(C_{2-3} alkyl), (C_{1-4} alkoxy)phenyl(C_{2-4} alkyl), or (C_{1-4} acyl)amino(C_{1-4} alkyl),

alk is C_{1-4} alkyl substituted by a 3 to 6 membered cycloalkyl group,

X is —O—, —S— or —SO_2—; and

R_1 is —C_{1-4} alkyl- or —C_{1-4} alkoxy-,

in their racemic and optically active forms, and their addition salts with pharmaceutically acceptable acids. These compounds are useful in therapy as β-adrenergic blocking agents. Intermediates are also provided.

1 Claim, No Drawings

ITEM 17. **DEBARMENT STATEMENT**

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic, Alcon Universal, Ltd., 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 application and all efficacy supplements)

NDA/BLA Number:	21114	**Trade Name:**	BETAXON(LEVOBETAXOLOL HCL OPHTHALMIC SUS
Supplement Number:		**Generic Name:**	LEVOBETAXOLOL HCL OPHTHALMIC SUSPENSION
Supplement Type:		**Dosage Form:**	Suspension/Drops; Ophthalmic
Regulatory Action:	AP	**Proposed Indication:**	for the lowering intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Safety and effectiveness in pediatric patients have not been established. The sponsor has been issued a Written Request to complete and submit studies by October 1, 2002 Pediatric Studies have been deferred. 2/23/00-

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LORI GORSKI

/S/ 2/23/00

Signature Date

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-114

Alcon Laboratories, Inc.
Attention: Susan H. Caballa
Director, Regulatory Affairs
6201 South Freeway, R7-18
Fort Worth, TX 76134-2099

OCT 15 1999

Dear Ms. Caballa:

Reference is made to to Alcon Universal, Limited's Proposed Pediatric Study Request submitted on August 25, 1999, for Betaxon (levobetaxolol hydrochloride ophthalmic suspension), 0.5% to NDA 21-114.

To obtain needed pediatric information on levobetaxolol hydrochloride for the treatment of elevated intraocular pressure, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following study:

Type of Study:
The study should be a randomized, double-masked, parallel comparison trial. The study should be of at least 12 weeks duration and should include a minimum of four evaluations including baseline and end of treatment.

Indication/Objective:
The primary objective of the study should be to evaluate the safety and the clinical response on elevated intraocular pressure between treatment groups. Enrolled patients should include male and female pediatric patients with a clinical diagnosis of glaucoma or elevated intraocular pressure.

Age Groups:
Pediatric patients should be less than 6 years of age. There should be at least 5 pediatric patients per arm per strata. The strata should consist of approximately 1 year intervals (i.e., between 1 week and 1 year, between 1 year and 2 years, between 2 years and 3 years, etc.).

Drug Information:
Levobetaxolol hydrochloride ophthalmic suspension, 0.5% should be compared to an appropriate control treatment.

Drug Specific Safety Concerns:
In addition to monitoring adverse events, vital signs, intraocular pressure, visual acuity, dilated ophthalmoscopy, and corneal diameter should be performed at baseline and end of therapy. Particular attention should be made to evaluate the drug product's effects on safety evaluations of pulse, blood pressure, and alertness.

Statistical Analysis:
At least 30 patients per arm should be enrolled.

Labeling:
Appropriate sections of the label may be changed to incorporate the finding(s) of the study.

Format of Reports To Be Submitted:
A full study report providing the analyses outlined in this request should be provided at the completion of this study. The report, which has not previously been submitted to the Agency, should include the complete analysis, assessment, and interpretation of the study.

Timeframe:
The report of the above study must be submitted to the Agency on or before October 1, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit the protocol for the above study to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

The report of this study should be submitted as a new NDA or as a supplement to an approved NDA, with the proposed labeling you believe would be warranted based on the data derived from this study. When submitting the report, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS-PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or mail/messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, Maryland 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your applications. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Joanne Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

/S/ 15 October 1999

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
IND
NDA 21-114
HFD-550 Div Files
HFD-550/Dep Dir/Chambers
HFD-550/Clin Rev/Holmes
HFD-550/SCSO/Zeccola
HFD-550/Proj Mgr/Gorski
HFD-105/ADRA/Walling
HFD-600/Office of Generic Drugs
HF-2/Lumpkin
HFD-104/DMurphy
HFD-002/T.Crescenzi

/S/ 10/6/99 /S/ 9/13/99 /S/ 9/14/99 /S/ 9/10/99

Drafted by: jh/September 3, 1999
Filename: n21114pedrequest.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

EXCLUSIVITY SUMMARY for NDA # 21-114 SUPPL #_____

Trade Name Xyzal Generic Name levocetirizine dihydrochloride

Applicant Name Alcon Universal Ltd. HFD- 550

Approval Date, if known _____

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 question about the submission.

   a) Is it an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   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 /X/ 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:

   _____

   _____

d) Did the applicant request exclusivity?

YES /X/ NO /___/

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

5 years

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? (Rx-to-OTC switches should be answered NO-please indicate as such.)

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 /X/

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 /X/ NO /___/

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

NDA# 19-270 Betoptic

NDA# 19-845 Betoptic-S

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 /___/ N/A

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

NDA# _____ N/A

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 /X/ 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 what is already known 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.

(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 /X/ 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:

_____

_____

YES /___/ NO /___/

(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 /X/

(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 /X/

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:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 C97-67 YES /___/ NO /_X_/

Investigation #2 C97-80 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

(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 /X/

If yes, explain: _____

/S/ 2/14/00

Signature Date

Title: MEDICAL OFFICER

/S/ 2/17/00

Signature of Division Director Date

Deputy

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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 # [redacted] YES /X/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # [redacted] YES /X/	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 _____
_____	_____
_____	_____

DUPLICATE

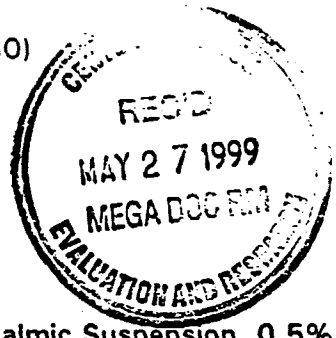
M

Alcon
LABORATORIES

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

May 25, 1999

Division of Analgesic, Anti-Inflammatory,
and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852



Re: **NDA 21-114**
Levobetaxolol Hydrochloride Ophthalmic Suspension, 0.5%
Original New Drug Application – User Fee ID

Dear Sir/Madam:

As an authorized U.S. representative of Alcon Universal, Ltd. (AUL), I hereby submit a New Drug Application (NDA) for Levobetaxolol Hydrochloride Ophthalmic Suspension, 0.5%. This NDA is being submitted pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54. The drug product is indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Consistent with our discussions at our pre-NDA meeting on May 5, 1999, this is a pre-submission of the Chemistry, Manufacturing and Controls (Part 4-CMC) and Aseptic Manufacturing Process (Part 7-Microbiology) sections. Within 120 days of this date, the full NDA which will include the remaining sections (Summary, Proposed Labeling, Preclinical, Clinical/Statistical) will be submitted.

The application consists of an Archival and Technical Review copy. The Archival copy consists of 8 volumes. A Table of Contents of the CMC and Microbiology sections is provided in each volume. An extra review copy of the Microbiology section is being provided for the Microbiology reviewer.

We are holding three copies of the Methods Validation Package and will send them upon FDA request. I certify that a true copy of the CMC and Microbiology sections has also been sent to the District Office in Dallas, Texas.

Establishment Information: A list of all facilities listed in this application is included as an attachment to the Form FDA 356h. All the facilities listed are ready for inspection.

Letters of Authorization: Letters of authorization to cross reference all NDAs and DMFs listed in this application follow the establishment information.

Pagination: The document is consecutively paginated in the lower right hand corner. The page number is made up of two parts. An example is page "4-0044". The "4" represents the item number corresponding to Part 4, Chemistry Section and "0044" is the consecutive page number within the Chemistry section.

CANDA: An electronic file of the CMC and Microbiology sections will be provided on CD-ROM under separate cover to Ms. Lori Gorski, Project Manager. Please note that since the hard paper copies were generated from the electronic file, signatures on some documents were not reproduced. Signed copies of documents are on file and are available upon request.

If you require additional information, I may be reached at (817) 568-6296.

Sincerely,

Susan H. Caballa

Susan H. Caballa
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

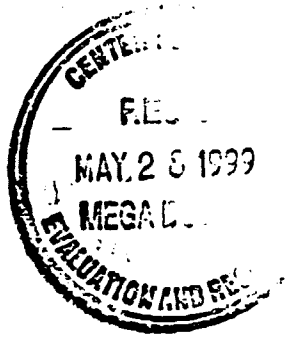
Airborne Airbill
#480-3280-834

ORIGINAL
NC

Alcon
LABORATORIES

NEW CORRESP

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450



May 26, 1999

Ms. Lori Gorski
Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: **NDA 21-114**
Levobetaxolol Hydrochloride Ophthalmic Suspension, 0.5%
Desk Copy of Electronic File

Dear Ms. Gorski:

Please find enclosed a desk copy of the electronic version of the CMC section of the NDA for Levobetaxolol HCl Ophthalmic Suspension submitted on May 25, 1999. The electronic version is being provided to you in both the PDF and WORD formats. Also enclosed are copies of the two Table of Contents included in the paper version of the NDA: one which provides volume and page information and another one which provides a listing of all the electronic document numbers.

If you require additional information, I may be reached at (817) 568-6296.

Sincerely,

Susan H. Caballa
Director
Regulatory Affairs

548.fda

Airborne #
851 5447 360

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

August 25, 1999

Wiley A. Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory,
and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: **NDA 21-114**
Levobetaxolol Hydrochloride Ophthalmic Suspension, 0.5%
Original New Drug Application – User Fee ID [redacted]

Dear Dr. Chambers:

On May 25, 1999, the Chemistry, Manufacturing and Controls (Part 4-CMC) and Aseptic Manufacturing Process (Part 7-Microbiology) sections of NDA 21-114 were submitted as per our agreement at the May 5, 1999 pre-NDA meeting. Following please find the remaining sections of the NDA (Summary, Proposed Labeling, Preclinical, Clinical/Statistical, Patent and Exclusivity Information, Patent Certification, Pediatric Use Information, Financial Disclosure/Certification, Debarment Certification). This NDA is being submitted pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54.

The application consists of an Archival and Technical Review copy. The Archival copy consists of 34 volumes. An index of the different sections is provided in each volume. The volume numbers start with volume 1 again. The Technical Review copy consists of volumes for:

Summary Volume
Nonclinical Pharmacology/Toxicology
Human Pharmacokinetics
Clinical

Twenty (20) additional copies of the summary volume (volume 1) will be sent as desk copies to Ms. Lori Gorski, Project Manager.

Pagination: The document is consecutively paginated in the lower right hand corner. The page number is made up of two parts. An example is page "8-0044". The "8" represents the item number corresponding to Part 8, Clinical Data Section and "0044" is the consecutive page number within the Clinical section.

CANDA: The following electronic files are being provided on CD-ROM disks as a desk copy under separate cover to Ms. Lori Gorski, Project Manager.

- Case Report Tabulations in Excel spreadsheets
- Clinical Biostatistics Programs and SAS Data Sets
- Electronic Files of the entire NDA sections in this submission in both Word 97 and PDF format. Please note that since the hard paper copies were generated from the electronic file, signatures on some documents were not reproduced. Signed copies of documents are on file and are available upon request.

GLP Compliance Statement: A statement listing all the nonclinical toxicology studies conducted under GLP may be found in archival volume 5, page 5-01238.

Data Cut-off Date for Safety Analysis: June 16, 1999

If you require additional information, I may be reached at (817) 568-6296.

Sincerely,

Susan H. Caballa

Susan H. Caballa
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 7 1999

NDA 21-114

Alcon Laboratories, Inc.
Attention: Susan H. Caballa
Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Ms. Caballa:

We have received Alcon Universal, Limited's new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Betaxon (levobetaxolol hydrochloride ophthalmic suspension) 0.5%

Therapeutic Classification: Priority (P)

Date of Application: August 25, 1999

Date of Receipt: August 26, 1999

Our Reference Number: NDA 21-114

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 25, 1999, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, contact Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 9/7/99

Anthony Zeccola
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 21-114
HFD-550/Div. Files
HFD-550/CSO/Gorski /S/
HFD-550/MO/Boyd
HFD-550/Chem/Fenselau
HFD-550/P/T/
HFD-550/PK/Tandon
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: /Sept 2 , 1999

filename: 21114ack

ACKNOWLEDGEMENT (AC)

ORIGINAL

ORIG AMENDMENT

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 04 1999
MEDIA DOC RM

October 1, 1999

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Re: **NDA 21-114 BETAXON™ (levobetaxolol HCl ophthalmic suspension) 0.5%**
Amendment to a Pending NDA

Dear Dr. Chambers:

Following please find our response to the chemistry and regulatory issues received via telefax on September 21, 1999. We have been working closely with SYLACHIM, our drug substance supplier, in addressing the issues raised on their DMF. They will be able to respond to issues 1 and 2 by October 15, 1999 but will require additional time to provide the response to issue 3. Their commitment is to have a response for issue 3 by the end of October 1999.

If you require additional information, I may be reached at (817) 568-6296.

Sincerely,

Susan H. Caballa

Susan H. Caballa
Director
Regulatory Affairs

563.fda

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

October 15, 1999

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Re: **NDA 21-114 BETAXON™ (levobetaxolol HCl ophthalmic suspension) 0.5%**
Amendment to a Pending NDA

Dear Dr. Chambers:

Following please find the following information as requested by the chemistry reviewer's request of today:

1. Copy of the publication by Kierstead et al., J. Med. Chem. 26: 1561 (1983)
2. Copy of the publication by Sharpless et al., JOC 54: 1295 (1989)
3. Letter of Authorization to DMF No. 5464.

If you require additional information, I may be reached at (817) 568-6296.

Sincerely,

Susan H. Caballa
Director
Regulatory Affairs

566.fda

October 20, 1999

Scott Krueger
Senior Director, Regulatory Affairs

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: NDA 21-114
Betaxon 0.5% Ophthalmic Suspension
Transfer of responsibility of Responsible Agent

Dear Ms. Gorski,

As you are aware, Ms. Susan Caballa has elected to terminate her position of Director Regulatory Affairs with Alcon Research, Ltd. effective October 29, 1999 in order to accept the position of Vice-President Regulatory Affairs for another pharmaceutical company.

This correspondence and attached form 356H confirms that I am accepting responsibility as the Responsible Agent for NDA 21-114, Betaxon 0.5% Ophthalmic Suspension.

Comments or questions concerning this NDA should be directed to my attention at 817/568-6116 or by fax at 817/551-4630.

Sincerely,

Scott Krueger

SK/bw

Alcon
RESEARCH, LTD.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

December 2, 1999

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: NDA 21-114
Betaxon 0.5% Ophthalmic Suspension
Response to Request for Information from the Pharmacologist.

Dear Ms. Gorski,

In response to your telephone request of November 9 conveying requests for additional information, I am please to provide you the requested information.

If you have any questions or comments concerning this additional information, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

SK/bw
Attachment
Airborne 9261493065

Via Telefax

NDA ORIG AMENDMENT

Alcon RESEARCH, LTD.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

/S/
Rec'd
12/2/99

December 7, 1999

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: **NDA 21-114**
Betaxon 0.5% Ophthalmic Suspension
Response to PK reviewer's request for clarification

Dear Ms. Gorski,

In partial response to the Pharmacokinetic reviewer's request for points of clarification of November 19, 1999, please find attached the information for item #3. Responses to items 1 and 2 should be available within a few days.

If you have any questions or comments concerning this response, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

ORIGINAL

SK/bw
Attachment
Airborne 9261493360

Via Telefax

NDA ORIG AMENDMENT

B D

Alcon
RESEARCH, LTD.

December 8, 1999

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: **NDA 21-114**
Betaxon 0.5% Ophthalmic Suspension
Response to PK reviewer's request for clarification

Dear Ms. Gorski,

In response to the Pharmacokinetic reviewer's request for points of clarification of November 19, 1999, please find attached the information for items #1 and 2. Response to item #3 was forwarded to you yesterday via telefax and courier.

If you have any questions or comments concerning these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

ORIGINAL

SK/bw
Attachment
Airborne 9261493360

/S/ Rec'd 12/14/99

NDA ORIG AMENDMENT

BC

Alcon
RESEARCH, LTD.

December 13, 1999

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: **NDA 21-114**
Betaxon 0.5% Ophthalmic Suspension
Response to Chemist's request for clarification

Dear Ms. Gorski,

Please find attached our responses to Dr. Tso's requests for clarification dated November 8 and November 10, 1999. Also provided as a desk copy for Dr. Tso are both a hard copy and a WORD version of these responses. Responses to Dr. Tso's request for clarification of November 22nd are in preparation and should be available within a few days.

If you have any questions or comments concerning these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

DESK COPY: Dr. Su Tso (responses and disk)
SK/bw Attachment
Airborne 9261493566

ORIGINAL

December 17, 1999

Alcon
RESEARCH, LTD.

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

NDA DRUG AMENDMENT
BC

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: NDA 21-114
Betaxon 0.5% Ophthalmic Suspension
Response to Chemist's request for clarification

Dear Ms. Gorski,

Please find attached our responses to Dr. Tso's request for clarification dated November 22 and telephone request of December 9, 1999. Also provided as a desk copy for Dr. Tso are both a hard copy and a WORD version of these responses.

If you have any questions or comments concerning these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger,
Senior Director
Regulatory Affairs

DESK COPY: Dr. Su Tso (responses and disk)
SK/bw Attachment
Airborne 4803400431

ORIGINAL

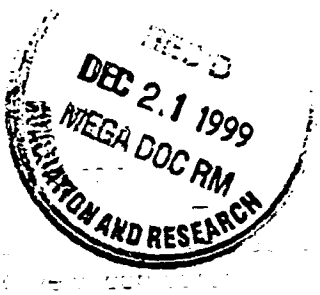
Alcon
RESEARCH, LTD.

December 20, 1999

6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

NEW CORRESP
NC

Ms. Lori Gorski
Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850



Re: NDA 20-114
BETAXON™ 0.5% Ophthalmic Suspension
Response to Chemist's Inquiry

Dear Ms. Gorski:

This amendment is to address the clarification question posed by Dr. Tso on December 17, 1999 concerning the formulation. The components of our formulation have not changed since the filing of IND [redacted]

If you require additional information, please contact me at 817-551-4517.

Sincerely,

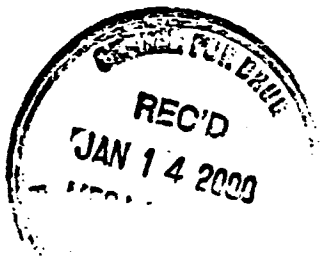
Sarah J. Cantrell
Manager, Regulatory Affairs

Airborne #
480 3400 033

ORIGINAL

VIA TELEFAX

January 12, 2000



Alcon
RESEARCH, LTD.

Scott Krueger
Senior Director, Regulatory Affairs
Tele: 817/568-6116 Fax: 551-4630

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

NC

Re: NDA 21-114
Betaxon 0.5% Ophthalmic Suspension
Response to Medical Officer

Dear Ms. Gorski,

Following is our response to the issues received today from the Medical Officer.

The principal investigator for study C-97-68 was Thomas L. Hunt, M.D., Ph.D. Dr. Hunt was incorrectly listed as Robert Hunt, M.D. on page 8-00837 of the Clinical Study Report and on page 16-00005 of the Financial Certification or Disclosure Statement. The completed financial disclosure form in our study files reflects the correct name of Thomas L. Hunt.

The study plan for Protocol C-97-40 on page 8-02131 incorrectly listed a 12 noon visit at the Eligibility 2 visit. The study flow chart on page 8-02969 is correct indicating that the Eligibility 2 visit consisted of only 8 am and 10 am visits.

If you have any questions or comments concerning these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

DUPLICATE

SK/bw

Alcon
RESEARCH, LTD

January 18, 2000

Scott Krueger
Senior Director, Regulatory Affairs
Tele: 817/568-6116 Fax: 551-4630

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

54

Re: NDA 21-114
Betaxon 0.5% Ophthalmic Suspension
Four-Month Safety Update

Dear Ms. Gorski,

Please find enclosed our Four-Month Safety Update for Betaxon (Levobetaxolol HCl 0.5% Ophthalmic Suspension).

Included in this submission is an update of our clinical safety experience as well as a preliminary study report for Protocol C-97-82, our long-term comparative study versus timolol 0.5%.

As a desk copy for the Medical Reviewer, I am also providing data sets and electronic copies of the Safety Report and the Clinical Report for Protocol C-97-82.

If you have any questions or comments concerning these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director, Regulatory Affairs

DUPLICATE

DESK COPY: ATTENTION: LORI GORSKI, AIRBORNE #1540340955

SK/bw....Airborne #1540341154

January 24, 2000

Alcon
RESEARCH

Scott Krueger
Senior Director, Regulatory Affairs
Tele: 817/568-6116 Fax: 551-4630

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: NDA 21-114
Betaxon 0.5% Ophthalmic Suspension
Response to Chemist and Microbiologist

Dear Ms. Gorski,

Please find attached our responses to Dr. Fenselau's telefax of January 4, and to Dr. Tso's telefax of January 19, 2000.

Also, in response to Dr. Fenselau's comment of January 21, please be advised that Alcon's structure for compound D is correct. [redacted] has indicated that they will be correcting the structure of their [redacted]

If you have any questions or comments concerning these responses, please contact me at (817) 568-6116.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

DESK COPY: Dr. Su Tso and Dr. Fenselau
SK/bw Attachment
Airborne Express 1540341250

February 15, 2000

Alcon
RESEARCH LTD

Ms. Lori Gorski
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Scott Krueger
Senior Director, Regulatory Affairs
Tele: 817/568-6116 Fax: 551-4630

Re: NDA 21-114
Betaxon™ (levobetaxolol hydrochloride ophthalmic suspension 0.5%
Labeling Amendment

Dear Ms. Gorski,

In response to your telefax of January 28, 2000, please find attached Alcon's suggested revisions to the proposed insert text for BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5%. For your convenience, I am providing you, both in electronic and hardcopy formats, revised text reflecting through strikeouts and underlining where deletions and additions, respectively, have been made. In addition, a final proposed insert text is provided.

Alcon has the following comments on the proposed insert text as suggested by the FDA.

1. Alcon believes that it is appropriate that the calcium channel blocking effect of levobetaxolol be clearly identified in the labeling as a pharmacological activity. As summarized below and as presented in great detail in the NDA, the ocular levels of levobetaxolol substantially exceed those levels required to manifest calcium channel blocking activity in the eye. Additionally, these levels are maintained throughout the dosing interval for the product.

   Alcon believes that it is important to share valid scientific information concerning mechanisms of action of a drug with the medical community, even if the clinical relevance of this information is not yet fully understood.

   Alcon proposes that the following or similar statement be included within the Clinical Pharmacology section of the labeling.

DRAFT LABELING

Additionally, we propose to also include an appropriate cautionary statement in the Drug Interactions section of the labeling which states:

[redacted]

Summary of Supporting Information:
Levobetaxolol has been shown to inhibit voltage-dependent calcium channel activity in isolated vascular smooth muscle cells. The vasorelaxant action of levobetaxolol related to its calcium channel blocking has been demonstrated in multiple *in vitro* studies using porcine and bovine retinal arteries. In addition, a vasorelaxant action has been demonstrated for racemic betaxolol *in vitro* in ocular and non-ocular blood vessels from rat, guinea pig, rabbit, canine, bovine, porcine and human species. Racemic betaxolol has also been shown to have a peripheral vasorelaxant action *in vivo* in dogs and to increase optic nerve head blood flow in rabbits.

Levobetaxolol has been shown to bind specifically to calcium channel antagonist binding sites in rat cortical membranes and to reduce the influx of calcium elicited by an excitatory amino acid analog, N-methyl-D-aspartate (NMDA), in amphibian retinal ganglion cells and in fetal rat cortical neuron cultures. A protective action on retinal ganglion cells related to its calcium channel blocking activity has been shown for levobetaxolol against NMDA-induced cell loss in rats and ischemia-induced retinal dysfunction in rabbits *in vivo*. In a rat model of photo-oxidative-induced retinopathy, levobetaxolol completely prevented the retinal functional changes evident in the ERG and the structural damage observed in control animals.

It is significant to note that concentrations of levobetaxolol measured in iris/ciliary body of monkeys dosed for 30 days with 0.5% levobetaxolol ophthalmic solution were measured to be 174.8 micromolar (1 hr) and 349.5 micromolar (12 hr). These concentrations readily exceed the IC50s for beta blocking (IC50 = 2.39 micromolar) and calcium channel blocking activity (IC50 = 29.5 micromolar). Thus, both mechanisms of action of levobetaxolol may be clinically relevant and will be manifest in the eye and warrant disclosure to the medical community.

In addition to vasorelaxation by its action to block calcium channel activity in smooth muscle, Alcon believes that the calcium channel blocking activity of levobetaxolol may also be playing a role in modulating aqueous humor formation. The calcium channels in ciliary epithelial cells play a role in modulating the intracellular calcium activity and regulating calcium-mediated events in these cells, for example, the activation of potassium ion current. Also, calcium plays an important role in the operation of chloride channels in nonpigmented ciliary (NPE) epithelia. Thus, the inhibition of calcium entry to ciliary epithelial cells, while it may not have a major impact upon aqueous humor secretion, may modulate it and thereby contribute to this process thereby affecting the IOP. Calcium channel blockers, for example, verapamil and diltiazem, have been reported to reduce IOP in animals and humans.

The calcium channel blocking activity of betaxolol and levobetaxolol is well founded upon the results of binding and functional studies. Levobetaxolol inhibited the binding of the benzothiazepine, diltiazem, and the dihydropyridine, nitrendipine, tritiated calcium channel blockers to rat cortical membranes, in a dose-dependent manner. The IC_{50} values of levobetaxolol against diltiazem and nitrendipine binding were 19.2 micromolar and 29.5 micromolar, respectively. Timolol was 5 and 124 times less potent, respectively, compared to levobetaxolol at inhibiting their binding. The levobetaxolol concentrations achieved at 1 and 12 hours post-dose in the iris/ciliary body (ICB) of monkeys dosed for 30 days twice daily with 0.5% levobetaxolol ophthalmic suspension were 174.8 and 349.5 micromolar, respectively. These levels are from 6 to 18 times higher than the above IC_{50} values in the calcium antagonist binding experiments cited above.

A Ki value of 0.15 micromolar has been reported for levobetaxolol in blocking the activation of adenylate cyclase in rabbit ciliary processes. Thus, the concentration of levobetaxolol in the monkey ICB at 1 and 12 hours post-dose exceeds that required to inhibit isoproterenol-induced activation of adenylate cyclase, a beta-2 adrenergic receptor mediated event, by 1165 to 2330-fold. Therefore, topical levobetaxolol has the ability to block $beta_2$ adrenergic receptors and also calcium channels of the ICB when dosed in its proposed clinical concentration (0.5%) and dosage regimen (BID).

References:

Abelson MB, Mitchell Gilbert C, Smith LM. Sustained reduction of intraocular pressure in humans with the calcium channel blocker verapamil. Amer J Ophthalmol **105**:155-159, 1988.

Hirata K, Nathanson MH, Sears ML. Novel paracrine signaling mechanism in the ocular ciliary epithelium. Proc Natl Acad Sci USE **95**:8381-8386, 1998.

Jacob TJC, Civan MM. Role of ion channels in aqueous humor formation. Am J Physiol **271**:C703-C720, 1996.

Melena J, Santafe J and Segarra J. The effect of topical diltiazem on the intraocular pressure in betamethasone-induced ocular hypertensive rabbits. J Pharmacol Exp Therap **284**:278-282, 1998.

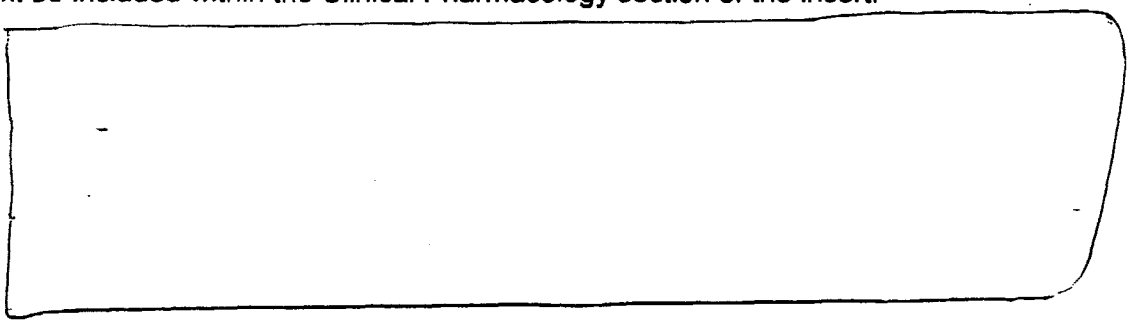
Melena J, Wood JPM, Osborne, NN. Betaxolol, a β_1-adrenoceptor antagonist, has an affinity for L-type Ca^{+2} channels. Eur J Pharmacol **378**:317-322, 1999.

Nathanson JA. Stereospecificity of beta adrenergic antagonists: R-enantiomers show increased selectivity for beta-2 receptors in ciliary process. J Pharmacol Exp Therap **245**:94-101, 1988.

Tang L-Q, Hong PH, Siddiqui Y, Sarkissian ES, Huang RY, Lee E, Krupin T. Effect of β-adrenergic agents on intracellular potential of rabbit ciliary epithelium. Curr Eye Res **17**:24-30, 1998.

APPEARS THIS WAY
ON ORIGINAL

2. Alcon believes that the Clinical Pharmacology section should reflect the results of the study conducted with BETAXON™ in subjects with reactive airway disease. The results of this study are clinically relevant and should be made available in the labeling to assist physicians in making a risk assessment as to whether BETAXON may be appropriate for use in individual patients due to pulmonary safety and quality of life concerns. Alcon also believes that this information should not be presented in a manner that encourages physicians not to consider the risks of treating glaucoma patients with reactive airway disease. Therefore, Alcon suggests that the following text be included within the Clinical Pharmacology section of the insert.



Supporting Information:
Alcon has conducted a specific controlled clinical study to assess the impact on BETAXON on pulmonary function. In this study, BETAXON was dosed (1 drop each eye) to 30 subjects with reactive airway disease who had demonstrated during screening at least a 15% reduction in FEV_1 (forced expiratory volume in one second) in response to a single drop (1 drop each eye) to a non-cardioselective beta-blocker (timolol). Per the American Thoracic Society, a 12-15% reduction in from baseline in FEV_1 is considered a clinically significant reduction. The results of this crossover study demonstrated that the mean percent change in FEV_1 from baseline for BETAXON was not significantly different from zero at any timepoint. In contrast, the mean percent change in FEV_1 observed for timolol was statistically different from zero (change in FEV_1 = -10.44%) by 15 minutes post dosing and was both statistically significant and clinically relevant (>15% decrease in FEV_1) at all timepoints measured from 30 minutes to 180 minutes post dosing. During this timeframe, the mean percent reductions in FEV_1 observed post timolol dosing ranged from 15% to 22.2%. Similar results were also observed in FVC (forced vital capacity) and FEV_1/FVC. This study confirms the results previously documented in a similar controlled clinical study conducted with 1% betaxolol solution.

3. Alcon believes that the Clinical Pharmacology section should include a statement concerning the no evidence of cardiac blockade during exercise. Alcon believes that the results of this study are clinically relevant and should be made available in the labeling to assist physicians in making a risk assessment as to whether BETAXON may be appropriate for use in individual patients due to quality of life concerns. Alcon also believes that this information should not be presented in a manner that encourages physicians not to consider the using topical beta blockers in glaucoma patients with severe cardiac dysfunction. Therefore, Alcon suggests that the following "balanced" text be included within the Clinical Pharmacology section of the insert.

Supporting Information:
Alcon conducted a controlled two-period crossover clinical study (BETAXON 0.5% versus timolol 0.5%) in 33 subjects, age ≥ 60 years. The purpose of this study was to confirm that movement from racemic betaxolol to levobetaxolol did not alter the conclusions from the previously conducted study which compared the affects of 1% betaxolol, timolol 0.5% and placebo on cardiovascular function during exercise. The results of this study are consistent with the results of the previous study and establish that BETAXON 0.5% has significantly less effect on heart rate, double product and blood pressure during exercise as compared to timolol 0.5% in subjects aged 60 and over.

We look forward to discussing these proposed labeling revisions with you during our teleconference at 9:00 a.m. (EST) on Thursday, February 17, 2000. Unless advised of a different phone number, I will call the (301) 827-2090. If you have any questions concerning this submission, please contact me at (817) 568-6116, or by fax at (817) 551-4630.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

SK/bw

DESK COPY: Lori Gorski

February 17, 2000

Alcon

Scott Krueger
Senior Director, Regulatory Affairs
Tele: 817/568-6116 Fax: 551-4630

Mr. Rafael Rodriguez
DAAODP
CDER, HFD-550
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD. 20850

Re: NDA 21-114
Betaxon™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5%
Final Draft Labeling

Dear Mr. Rodriguez:

Please find attached the final proposed insert text for Betaxon™. The text has been revised as discussed and agreed during our teleconference with the Division occurring this date.

In addition, please find attached final draft labeling for the container label and cartons which reflect revision of the in-storage temperature to be [redacted] requested by the Chemist as agreed in response to Issue #9 included in our letter dated December 17, 1999.

If you have any questions concerning this submission please contact me at 817/568-6116 or by telefax at 817/551-4630.

Sincerely,

Scott Krueger
Senior Director
Regulatory Affairs

SK/bw
Airborne Express 1540343652