CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-134

CORRESPONDENCE

2. Definitive Study

OBJECTIVE

To evaluate the bioequivalence of BLP tobramycin/dexamethasone to TobraDex, each as compared to placebo in reducing conjunctival hyperemia and ocular itching associated with acute allergic conjunctivitis induced by topical allergen challenge.

STUDY DESIGN

This study is a randomized, double-masked, placebo-controlled, evaluation of BLP tobramycin/dexamethasone and TobraDex in approximately 120 volunteers exposed to allergen challenge. Subjects will be randomized into two treatment arms (BLP tobramycin/dexamethasone:placebo and TobraDex placebo) and will receive active drug in one eye and placebo in the contralateral eye four times daily for xxx days. (This xxx dosing schedule determined from the pilot study will assure a margin of likelihood of achieving sufficient conjunctival hyperemia and ocular itching responses.) Conjunctival hyperemia and ocular itching will be assessed as the primary efficacy parameters, with a 0.5 unit clinical change and a statistical reduction being sought between each active drug and its placebo, while clinical bioequivalence is sought between the active drugs themselves. The study consists of three visits; Visit 1 (Day 0), Visit 2 (Day 7), and Visit 3 (Day 21). Note, the final design of this study may be modified based upon the results of the loading dose pilot study.

Reviewer's Comments:

As stated above, the design of this study is dependent on the results of the pilot study. Comments will therefore be deferred until the results of the pilot study are available, although the plan should be to evaluate a 1 unit change and the eyes should be treated independently instead of as a paired comparison.

Recommended Regulatory Action:

The study should be permitted to proceed with the modifications listed in this review. These comments have been discussed informally with the sponsor.

Wiley A. Chambers, M.D.
Ophthalmology, HFD-550

cc:

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

September 9, 1999

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%

Telephone Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the Agency's September 7, 1999 Telephone Amendment communicated to David Desris of Bausch and Lomb Pharmaceuticals, Inc. from Lynne Ensor, microbiologist in OGD for the above referenced application.

We intend to fill the Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1% product on filling '

Information for the January 9, 1991 process simulation media fill for lot #13004 is provided in Attachment 1.

Information for the February 25, 1994 process simulation media fill for lot # 503051 is provided in Attachment 2. . Lot #50305 was split filled first into a 2 mL fill/5.75 mL bottle and then a 60 mL fill/4 oz. bottle. The recertification summary for incorrectly listed lot #503051 as a 2 mL fill volume in a 5.75 mL bottle. Lot #503051 was a 60 mL fill volume/4 oz. bottle and lot # 503052 was a 2 mL fill volume/5.75 mL bottle. The additional number at the end of the lot is used to designate the fill volume. The recertification summary Lot #503051, date filled 2/25/94 has been corrected to read Container Size: 60 mL / 4 oz. and Fill Volume: 60 mL.

In accordance with 21 CFR 314.70(a)(5), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430. If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7700 ext. 7115 or facsimile (813) 975-7757.

Sincerely,
David Desris
David Desris R.Ph.
Manager,
Regulatory Affairs
Enclosure

Pharmaceuticals, Inc. 2500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

September 3, 1999

BAUSCH LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AF

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%

Labeling Amendment

Dear Sir or Madam:

This correspondence is submitted in response to your August 30, 1999 facsimile from the Division of Labeling and Program Support. As requested, the insert labeling has been revised and 12 copies are being submitted in final print. An insert side by side comparison of Bausch and Lomb Pharmaceuticals, Inc. Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1% with the reference listed drug Tobradex® is provided.

The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7700 ext. 7115 or facsimile (813) 975-7757.

Sincerely,

David Desris

David Desris R.Ph.
Manager,
Regulatory Affairs

Enclosure

August 18, 1999

NEW CORRESP
N/C

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%

(9,1) F

Telephone/Facsimile Amendment

Dear Sir or Madam:

Reference is made to our August 10, 1999 Facsimile Amendment and the August 17, 1999 telephone conference between Mark Anderson and Maria Shih with the FDA's Office of Generic Drugs and David Desris, Don Chmielewski, Ramesh Krishnamoorthy, and Mike Brubaker with Bausch and Lomb Pharmaceuticals, Inc.

In response to the Agency's query on consistent specifications for the related substances for Tobramycin drug substance (XA50283) received from Biogal, provided are the Certificates of Analysis for three recent separate lots which reflect monitoring and reporting of the related substances by Biogal. The three lots are Biogal lot no. O-50398 which corresponds to Bausch and Lomb lot no. 0104199, Biogal lot no. O-40698 which corresponds to Bausch and Lomb lot no. 0104099, and Biogal lot no. O-02298 which corresponds to Bausch and Lomb lot no. 0103999. The Biogal and Bausch and Lomb Certificate of Analysis for these lots are provided in Attachments 1, and 3 respectively. These related substances include nebramine, neamine, and kanamycin. The values reported by Biogal for the stated lot(s) are not significantly different than those determined by Bausch & Lomb.

It is to be noted that though the acceptance criteria set forth by Biogal is wider than those by Bausch & Lomb, it is our practice to reject material which does not meet our specification. Thus, we will continue to impose our specifications on this material and work with the vendor to revise their specifications with the progress of time. The Tobramycin drug substance is monitored by both parties for related substances.

In accordance with 21 CFR 314.70(a)(5), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7700 ext. 7115 or facsimile (813) 975-7757.

Sincerely,

David Desris

David Desris R.Ph.
Manager,
Regulatory Affairs

Enclosure

[redacted]

Pharmaceuticals, Inc. [illegible] Tampa FL 33637 [illegible] Fax 813 975 7770

August 10, 1999

BAUSCH & LOMB

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%

Facsimile Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the Agency's Facsimile Amendment dated July 26, 1999 for the above referenced application. To facilitate your review each of the observations and our corresponding response is provided.

Reference is made to your observation:

1. "Regarding bulk material Tobramycin:

CGD EVALUATION AND RESEARCH

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

8/10/99

and

* The time zero data is the same for Horizontal and Upright orientations.
**No Testing performed for the Upright sample.

In accordance with 21 CFR 314.70(a)(5), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7700 or facsimile (813) 975-7757.

Sincerely,

David Desris

David Desris R.Ph.
Manager,
Regulatory Affairs

Enclosure

April 22, 1999

BAUSCH & LOMB

Office of Generic Drugs
Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%

Bioequivalence Amendment

Dear Sir or Madam:

Reference is made to a phone conference with Dr. Wiley Chambers on April 7, 1999 concerning the addition of a control arm to the *In Vitro* Microbial Kill Rate Study comparing the reference listed drug, Tobradex® and Bausch and Lomb Pharmaceuticals, Inc. Tobramycin 0.3% and Dexamethasone 0.1% Ophthalmic Suspension.

An *In Vitro* Microbial Kill Rate Study was repeated using the bacteria indicated in the USP Antimicrobial Effectiveness Testing procedure and the Bausch and Lomb Pharmaceuticals package insert with a control arm added to the test procedure using sterile saline.

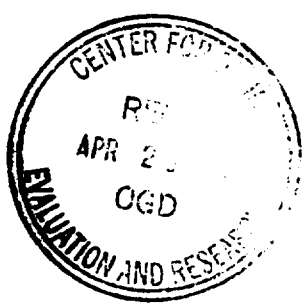
The Final Report study (Addendum to Protocol [illegible] nd supporting information is provided. A table of contents is provided on page 2 of 16 of the report for your reference.

Sincerely,

David Desris

David Desris R.Ph.
Manager
Regulatory Affairs

Enclosure



Pharmaceuticals, Inc. [illegible] Tampa FL 33637 813 975 7700 Fax 813 975 7770

January 20, 1999

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

[illegible]

Re: AADA 64-134 Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Gratuitous Amendment for
Alternate Container Sterilization Chamber

Global Supplement. Related Applications:

Dear Sir or Madam:

The purpose of this correspondence is to request approval of an alternate chamber for [illegible]erilization of container components. Specifically, we are seeking approval to use Sterilization Chamber #2,
This is a Global Supplement, affecting all applications listed above.

The new sterilization chamber is operated by the same company and is located at the same facility as the currently approved chamber. No other changes are requested in this application. Supporting documentation for the change is provided as an attachment to this letter. An index of the enclosed documentation is provided immediately following the form 356h.

In accordance with 21 CFR 314.70(a) , we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

We believe that this correspondence provides a thorough justification for the proposed change. As such, we hope that a rapid review and approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

RECEIVED
JAN 21 1999

Sincerely,
David Desris
David Desris R.Ph.
Manager,
Regulatory Affairs
Enclosure

Study Procedure:

This study consisted of three study visits; Visit 1 (Day 0), Visit 2 (Day 7), and Visit 3 (Day 21). During Visit 1, subjects who provided informed consent and met the study entry criteria were challenged bilaterally. Subjects who had a positive ocular allergic reaction after receiving the allergen (specifically 2+ hyperemia and 2+ itching score) returned for Visit 2. During Visit 2, it was confirmed that the positive reaction observed at Visit 1 was reproducible; these results also served as the baseline scores for the study. At Visit 2, 126 subjects were randomized to one of three loading regimens (2, 5 or 14 days), and subsequently into one of three treatment arms: BLP:placebo, TobraDex:placebo or BLP:TobraDex. Based on this randomization, approximately 14 subjects were enrolled into each treatment arm for each loading regimen.

Subjects were instructed to begin instilling one drop of the masked study medication into the appropriate eye four times daily for 2, 5 or 14 days prior to Visit 3. At Visit 3, one drop of the appropriate study treatment was instilled into the assigned eye of each subject. Three hours later, each subject received an allergen challenge (using the same allergen that elicited a positive response at Visit 2) and were evaluated at 3, 5, 10 and 15 minutes post-challenge for itching and at 10, 20, and 30 minutes for conjunctival hyperemia. IOP measurements were made following the 30 minute hyperemia evaluation. Subjects were re-challenged with the same allergen (as received at Visit 2) six hours after masked drug administration and were again evaluated in the same manner as the previous allergen challenge.

Entry Criteria:

Asymptomatic, healthy volunteers, 18 years old and older with a history of allergic conjunctivitis, and who met the study inclusion and exclusion criteria were enrolled into the study.

Demographics:

One hundred and twenty six (126) subjects ranging in age from 18 to 68 years (mean = 37 years), were enrolled into this study. There were 77 females and 49 males. The majority were Caucasian, and all subjects were from the New England area. The majority of subjects had brown eyes (n=49) or blue eyes (n=39). Frequency comparisons by treatment group demonstrated that there were no statistical differences for any of the demographic or baseline variables.

Patient Accounting:

Number of subjects screened:	207
Number of subjects randomized:	126
Number of subjects discontinued:	7
Number of subjects completed:	119
Number of subjects analyzed for efficacy	118
- BLP/placebo treatment arm	38
- TobraDex/placebo treatment arm	38
- BLP/ TobraDex treatment arm	42

Medical Officer's Review of ANDA 64-134

NDA 64-134

Submission Date: 1/14/99
Received Date: 1/20/99
Review Date: 2/11/99

Drug: Tobramycin and Dexamethasone Ophthalmic Suspension 0.3%/0.1%

Applicant: Bausch & Lomb
Pharmaceutical Division
8500 Hidden River Parkway
Tampa, FL 33637
(813) 975-7770

Submitted: Response to agency's deficiency letter dated November 17,1997. Response includes the results of Study 287-002.

Protocol Title: A Randomized, Double-masked, Placebo-controlled Comparison of the Clinical Bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. Tobramycin and Dexamethasone Ophthalmic Suspension, 0.3%/0.1% Compared to TobraDex in Volunteers Exposed to Allergen Challenge

Study Objective: This study was designed to assess the clinical bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. tobramycin and dexamethasone sterile ophthalmic suspension, 0.3%/0.1 % (BLP) and TobraDex sterile ophthalmic suspension in reducing conjunctival hyperemia and ocular itching associated with acute allergic conjunctivitis induced by topical allergen challenge.

Study Design: Randomized, double-masked, placebo-controlled, single center evaluation.

Principal Investigator: Jack V. Greiner, OD, DO, PhD
Ophthalmic Research Associates, Inc.
863 Turnpike Street
North Andover, MA 01 845

7 Whittier Place
Suite 105
Boston, MA 02114

Dosage:

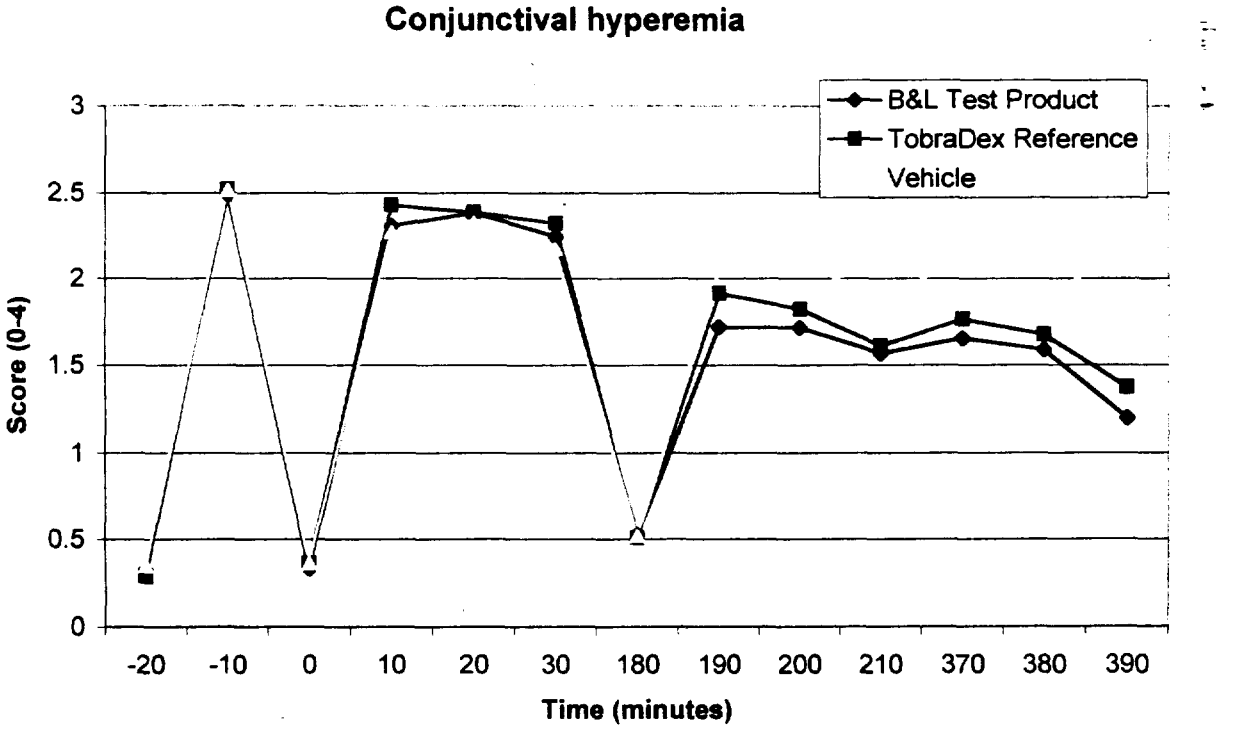
Bausch & Lomb Pharmaceuticals, Inc. tobramycin/dexamethasone sterile ophthalmic suspension contains tobramycin, 0.3% and dexamethasone, 0. 1 %. TobraDex sterile ophthalmic suspension (Alcon Laboratories, Inc.) contains tobramycin 0.3% and dexamethasone 0.1%.

Subjects were instructed to instill one drop (approximately 35 µl drop) of the assigned study medication (BLP, TobraDex or placebo) into the appropriate eye four times for 2, 5 or 14 days prior to Visit 3.

Efficacy Measures

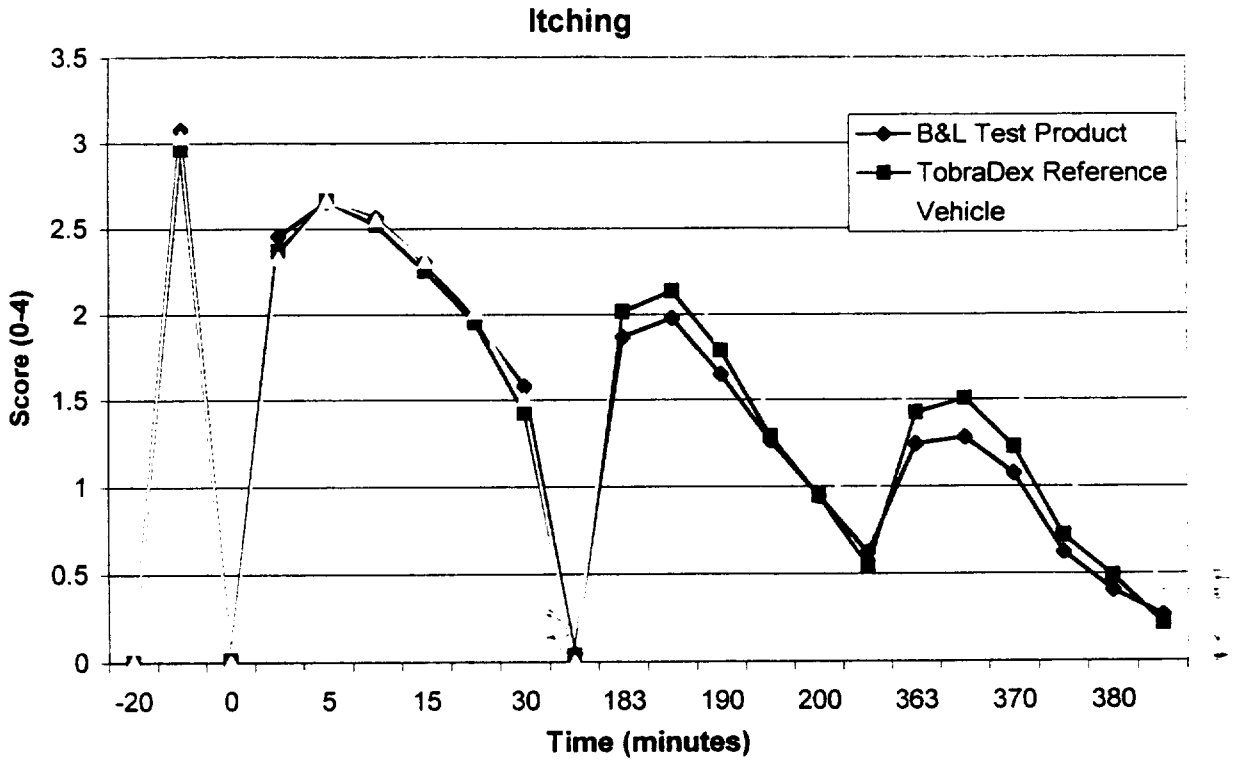
The primary efficacy measures for demonstration of clinical bioequivalence were conjunctival hyperemia and ocular itching. Secondary efficacy measures were ciliary and episcleral hyperemia, chemosis, lid swelling, tearing and mucous discharge.

Reviewer's Comments: *Concur with primary endpoints.*



Reviewer's Comments:

All three groups demonstrate equivalence prior to drug administration (prior to time 180). After drug administration, the B&L test product and the reference product clearly separate from vehicle and the test product is at least as effective as the reference product.



Reviewer's Comments:

All three groups demonstrate equivalence prior to drug administration (prior to time 180). After drug administration, the B&L test product and the reference product clearly separate from vehicle and the test product is at least as effective as the reference product.

Safety Measures

Adverse events, intraocular pressure (IOP), visual acuity and slit-lamp biomicroscopy parameters were evaluated as safety measures.

Reviewer's Comments: *Acceptable.*

Intraocular Pressure

Intraocular pressure (IOP) was measured at Visit 2 (baseline) and at Visit 3 (following the 6 hour allergen challenge). Only minor changes were observed across all eye treatments and loading regimens. The mean IOP at baseline was comparable across loading regimens and eye treatments as shown by analysis of variance with eye treatment ($p=0.939$), loading regimen ($p=0.094$) and their interaction as factors ($p=0.320$). Baseline mean IOP ranged from 14.1 to 16.2 mmHg

Reviewer's Comments: *The drug products were not administered long enough to see the known effects in steroid responders.*

Slit Lamp Findings

Slit lamp exams were performed at each of the study visits. No abnormal slit lamp exam findings were reported at any visit on the study.

Reviewer's Comments: *Concur.*

Adverse events

There were 24 adverse events reported by 22 out of 126 subjects (17.4%) enrolled into the study. Six events reported by 6 subjects had their onset after Visit 2 but prior to the scheduled start of study medication. These events included rhinitis, injury accident, back pain, headache, nausea and a cardiovascular disorder. One of these events was judged to be serious in nature. The additional five events were non-serious in nature and judged to be unlikely or unrelated to the study medication.

There were 18 treatment emergent events reported by 16 subjects, out of 125 treated with study medication, with onset after the scheduled start of study medication. The majority of the events involved the body as a whole (10) or digestive system (4). Three subjects (4 events) experienced events that were rated severe in intensity (back pain (2 events), migraine and headache). Of the remaining 14 events, 12 were rated as moderate and 2 were rated as mild.

Sixteen of the 18 events were judged to be unrelated or unlikely related to the study medication. The 2 events that were judged to be possibly related occurred in a single patient who reported burning and itching of their eye(s) after instillation of study medication at Visit 3.

Summary of Treatment Emergent Adverse Events: Frequency by Treatment Arm

Treatment Emergent Adverse Event Description	BLP/ Placebo (n=42)	TobraDex/ Placebo (n=42)	BLP/ TobraDex (n=42)
Pain Back	2 (4.8%)	0	0
Headache	2 (4.8%)	2 (7.1%)	1 (2.4%)
Nausea	1 (2.4%)	0	0
Flu symptoms	2 (4.8%)	0	0
Migraine	0	1 (2.4%)	0
Dyspepsia	0	1 (2.4%)	0
Rash	0	1 (2.4%)	0
Pain Neck	0	0	1 (2.4%)
Tooth disorder	0	0	2 (4.8%)
Burning/Stinging in eye	0	0	1 (2.4%)
Itching in eye	0	0	1 (2.4%)
TOTALS	7 (16.7%)	5 (11.9%)	6 (14.3%)

Reviewer's Comments: *The frequency of reported experiences is consistent with the experience from the reference product.*

Visual Acuity

Visual acuity (ETDRS chart) was assessed at each of the study visits. Only minor changes in visual acuity were observed during the study. Results indicate that visual acuity was similar between treated eyes (BLP treated eyes, TobraDex treated eyes or placebo treated eyes) across loading regimens. The mean change from baseline for the ETDRS scores ranged from 0.02 to 0.47. Across all loading regimens, approximately 95% of the treated eyes experienced a change from baseline in visual acuity of less than 0.2. There were 9 treated eyes (4-BLP, 2-TobraDex, 3-placebo treated eyes) that experienced a change from baseline in visual acuity of greater than 0.2 (approximately 2 line Snellen change). Overall the visual acuity changes in all treated eyes were consistent. In addition, the visual acuity changes in the BLP and TobraDex treated eyes were comparable.

Reviewer's Comments: *Concur.*

Conclusions:

1. The corticosteroid component of the test product has been demonstrated to be at least as effective in the test product formulation as the corticosteroid component of the reference product.

2. The anti-infective component of the test product should be evaluated in an *in-vitro* "kill curve" model with appropriate reference controls (positive and negative).

3. No new safety concerns (beyond those already known for the reference product) have been identified in the submitted information.

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

Cc:

HFD-550/Chambers

January 14, 1999

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%

BIOEQUIVALENCE STUDY

Dear Mr. Greenberg:

The purpose of this correspondence is to provide a copy of the Bioequivalence study (Attachments 13 and 14) and cover letter that were submitted in the December 10, 1998 Major Amendment response. This was requested to David Desris in a phone conversation on January 13, 1999.

If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 Ex. 7115.

Sincerely,

David Desris

David Desris, R.Ph.
Manager
Regulatory Affairs

RECEIVED
JAN 20 1999
GENERIC DRUGS

Enclosure

December 10, 1998

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Major Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the agency's letter, dated November 17, 1997, for the above referenced application.

To facilitate your review, each of the observations and our corresponding response is provided below. Necessary supportive documentation is also provided for each response in the attachments. An index with the attachment number, content, and corresponding page number is provided for your reference.

Reference is made to your observations:

A. Chemistry

procedures.

Page(s) 5

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

12/10/98

We believe this correspondence provides a thorough response to the questions raised in the agency's November 17, 1997 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming.

In accordance with 21 CFR 314.70 (a) we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 or by fax at (813) 975-7757.

Sincerely,

David Desris

David Desris, R.Ph.
Manager
Regulatory Affairs

Enclosure

Pharmaceuticals, Inc.
Tampa FL 33637
Fax 813 975 7770

BAUSCH
& LOMB

April 3, 1998

BIOAVAILABILITY
ORIG AMENDMENT

Office of Generic Drugs
Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment

A randomized, double-masked, placebo-controlled comparison of the clinical bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. tobramycin and dexamethasone ophthalmic suspension, 0.3%/0.1%, compared to TobraDex® in volunteers exposed to allergen challenge

Gentlemen:

Reference is made to the above Abbreviated Antibiotic Drug Application.

To recap the bioequivalence process to date, in September, 1997, we received a communication that the drug product did not meet the criteria of "clinical bioequivalence" based on the review of the data by the medical consultant, Dr. Wiley Chambers. Since that time, we have been working with Dr. Chambers to revise the clinical model to assess this ophthalmic drug product. We recently completed our revisions to the model, and, after we obtain final concurrence from Dr. Chambers, expect to initiate a second definitive clinical bioequivalence study in the coming weeks. (See enclosed protocol.)

As we approach this large clinical study, we would like to clarify with you that the Office of Generic Drugs is continuing to follow the guidance of your medical consultants during the application approval process. We have dedicated much time and resources working with Dr. Chambers and the Office in developing a model system and criteria for "clinical bioequivalence" for this drug product (and other members in its class).

RECEIVED

APR 0 6 1998

GENERIC DRUGS

Pursuant to the initiation of this second definitive clinical bioequivalence study, enclosed is a copy of Protocol No. BLP 287-002, "Randomized, Double-Masked, Placebo-Controlled Comparison of the Clinical Bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. Tobramycin and Dexamethasone Ophthalmic Suspension, 0.3%/0.1%, Compared to TobraDex® in Volunteers Exposed to Allergen Challenge".

We look forward to submitting the results of this study in the near future. Thank you for your time and assistance, please do not hesitate to contact us if you have any questions regarding the study.

Sincerely,

David Mottola, PhD
Sr. Manager, Clinical and Scientific Affairs
phone - (813) 975-7703

Donald H. Chmielewski, RPh
Director, Regulatory Affairs
phone - (813) 975-7786

Enclosure

cc:

10/ 30/1997

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 64-134 APPLICANT: Bausch & Lomb

DRUG PRODUCT: Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%.

Reference is made to the proposed bioequivalence study protocol, submitted to the Office of Generic Drugs (OGD) for review, dated October 3, 1997. The protocol has been reviewed by the Division of Bioequivalence and the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products and we have the following comments for your consideration:

1. The study design is acceptable, however, in general, it is preferable to have each eye treated independently instead of a paired comparison.

2. The study should attempt to determine the dosing regimen necessary to elicit a 1 unit change in itching and a 1 unit change in redness.

3. At least 2 of the evaluations for itching and redness (hyperemia) should overlap in time. It is recommended that itching be evaluated at 5, 10, and 15 minutes.

4. The design of the study is dependent on the results of the pilot study. Comments will therefore be deferred until the results of the pilot study are available, although the plan should be to evaluate a 1 unit change, and the eyes should be treated independently instead of as a paired comparison.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 30 1997

BIOEQUIVALENCY AMENDMENT

ANDA: 64-134

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: Bausch & Lomb
ATTN: Donald Chmielewski

PHONE: (813) 975-7700
FAX: (813) 975- ~~7770~~ 7757

FROM: Lizzie Sanchez, Project Manager (301-827-5847)

Dear Sir:

This is in reference to the bioequivalency data submitted on October 3, 1997, pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

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Healthcare and Optics Worldwide

Noted: This piece has been consulted to Dr Chambers
M. Anderson

October 3, 1997

Office of Generic Drugs
Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment

A randomized, double masked, parallel group, contralateral eye comparison of the bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. (BLP) tobramycin/dexamethasone ophthalmic suspension compared to TobraDex® ophthalmic suspension in volunteers exposed to allergen challenge (BLP-9608)

Gentlemen:

Reference is made to the above Abbreviated Antibiotic Drug Application, and to the September 19, 1997 correspondence (attached) from the Division of Bioequivalence.

Pursuant to recent conversations between Dr. Mark Abelson (Ophthalmic Research Associates), Dr. David Mottola (Bausch & Lomb Pharmaceuticals, Inc. [BLP]) and Dr. Wiley Chambers, enclosed is a copy of a letter that addresses the concerns raised by Dr. Chambers regarding the results of bioequivalence study BLP-9608. The letter discusses Dr. Chambers' concerns as they pertain to the model system, revisions to the model and the strategy for moving forward to demonstrate the bioequivalence of BLP tobramycin and dexamethasone ophthalmic suspension, 0.3%/0.1% compared to TobraDex® ophthalmic suspension.

We look forward to discussing Dr. Chambers' review of our proposal for future studies. Thank you for your time and assistance, please do not hesitate to contact us if you have any questions regarding the study.

Sincerely,

David Mottola, PhD
Manager, Clinical Affairs
phone - 813 975-7700 ext. 7171

Donald H. Chmielewski, RPh
Director, Regulatory Affairs
phone - 813 975-7700 ext. 7203

Enclosure

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Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

July 1, 1997

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Office of Generic Drugs
Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRES
NC / BIO
mem of BIOAVAILABILITY

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment - *A randomized, double masked, parallel group, contralateral eye comparison of the bioequivalence of Bausch & Lomb Pharmaceuticals, Inc. (BLP) tobramycin/dexamethasone ophthalmic suspension compared to TobraDex® ophthalmic suspension in volunteers exposed to allergen challenge (BLP-9608)*

Gentlemen:

Pursuant to a recent conversation between Dr. Ellen Strahlman (Bausch & Lomb) and Dr. Wiley Chambers, enclosed is a letter that addresses the bioequivalence of the itching response in study BLP-9608. The letter and accompanying attachments review the bioequivalence data and discuss the clinical parameters assessed in the allergen challenge model that are most relevant to corticosteroid effects.

We look forward to discussing the results of Dr. Chamber's review of this submission and the overall bioequivalence submission. Thank you for your time and assistance, please do not hesitate to contact us if you have any questions regarding the study.

Sincerely,

David Mottola, PhD
Manager, Clinical Affairs
phone - 813 975-7700 ext. 7171

Donald H. Chmielewski, RPh
Director, Regulatory Affairs
phone - 813 975-7700 ext. 7203

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June 23, 1997

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Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Gratuitous Amendment

Dear Sir or Madam:

The purpose of this correspondence is to correct an oversight in Method was submitted in the May 16, 1997 Major Amendment response to the agency's letter dated December 27, 1996 for the above referenced application.

On page 084 of the May 16, 1997 submission (page 8 of 15 of ..... the correction factor used in the related substance calculation for the percent of Nebramine was stated as "1.34" . The correction factor should have been "0.75" , which is 1 divided by 1.34.

This is the only change made to Method using the 0.75 correction factor. Method All testing performed was completed with this revision is provided.

If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 or by fax at (813) 975-7757.

Sincerely,

David Desris

David Desris, R.Ph.
Manager
Regulatory Affairs

Enclosure

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Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

May 16, 1997

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Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Major Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the agency's letter, dated December 27, 1996, for the above referenced application.

To facilitate your review, each of the observations and our corresponding response is provided below. Necessary supportive documentation is also provided for each response in the Attachments. An index with the attachment numbers, contents, and corresponding page numbers in this amendment is provided for your reference. As requested, a copy of the December 27, 1996 letter is provided in Attachment 1. Bioequivalence deficiencies (B) were responded to in our February 14, 1997 amendment.

Reference is made to your observations:

Observation 1: " Proposed Acceptance Specifications for bulk drug substance, Final Product Specification Limits, and Stability Specifications should be based upon primary data, i.e. testing results for the drug substance lots utilized and the exhibit batches of drug product prepared in support of the submission. Specification limits on other approved drug products should be considered as supporting data, due to varying assay methodologies and other potential differences. These proposed specifications are understood to be based upon current data and are subject to revisions should additional data justify the change."

Response:

We acknowledge the reviewer's comments that Proposed Acceptance Specifications for bulk drug substance, Final Product Specification Limits, and Stability Specifications should be based upon primary data, i.e. testing results for the drug substance lots utilized and the exhibit batches of drug product prepared in support of the submission. Consequently, please refer to the response to Observation #2 for the appropriate specifications for the drug substance and drug product, based upon testing results for the drug substance and the exhibit batch for Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%.

MAY 19 1997

Observation 2: "With regard to the revised assay procedure , please provide an example(s) of a sample assayed by the former procedure and also assayed by the revised procedure. Please include the relevant calculations for the impurity levels. You state that the revised method does not require validation since the only difference is the run time. In view of the fact that the earlier procedure was not adequately validated, you should provide validation data for the revised procedure."

Response:

Sample Analysis and Relevant Calculations

With regard to the referenced assay procedures, chromatograms and calculations for the revised assay procedure and the former procedure re provided as follows:

- Example chromatograms of samples assayed by Attachment 2), which illustrates the extension of the run time to capture a late eluding peak;
- Relevant calculations for impurities levels are as follows:

(1) Individual Related Substances:

Each individual related substance above the limit of quantitation (LOQ, 0.1% label claim) is calculated using the following equation:

R_{Toby}

where,

R_{RS} = peak area response of the related substance
R_{Toby} = peak area response of tobramycin
RRF = relative response factor (see Table 1 below)

The response of individual related substances are corrected using the relative response factor (RRF). Relative response factors for the identified impurities and degradation product , are listed in Table 1. A RRF of 1.00 will be applied to any unknown related substance.

Table 1
Relative Response Factors (RRF) for Related Substances

Peak Identity	Relative Retention Time	RRF

(2) Total Related Substances:

The percent total related substances in the finished product is the summation of all individual related substances at or above the LOQ divided by the summation of all individual related substances at or above the LOQ including tobramycin.

where,
R_R = sum of all %Related Substances above the LOQ
R_T = sum of all %Related Substances above the LOQ and tobramycin

Method Validation

With regard to the referenced assay procedures, the former procedure was not adequately validated in the related substances range of 0.1 - 10% label claim. Validation data for the revised procedure is provided in Attachment 3, which demonstrates its ability to reliably measure related substances down to 0.1% (Method Validation: The additional validation data includes limit of quantitation, linearity, precision, accuracy, and specificity at the 0.1% level.

Revised Specifications

Observation #3: "On page 358 of your November 17, 1995 submission you note that the potency of active ingredient was not included as an in-process-control due to time considerations. These data are useful in demonstrating homogeneity and retrospective analyses of homogeneity problems and should be included in your validation batches, although not necessarily in the same time frame."

Response:

As requested, enclosed with this response is an In-Process Testing Summary which includes testing for tobramycin (methoc and dexamethasone (method ctive ingredients in the drug product (Attachment 5). In-Process testing for the active ingredients will be included in the validation batches only to demonstrate homogeneity for the drug product.

We believe this correspondence provides a thorough response to the questions raised in the agency's December 27, 1996 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming.

If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 or by fax at (813) 975-7757.

Sincerely,

David Desris

David Desris, R.Ph.
Manager
Regulatory Affairs

Attachments

Pharmaceutical Division [illegible] Tampa FL 33637 [illegible] Fax 813 975 7770

Noted: PAE - Assigned to Dr. Anderson for review. M Anderson 4/20/97

BAUSCH & LOMB
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April 15, 1997

Office of Generic Drugs
Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

BIOAVAILABILITY

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment

Gentlemen:

On April 27, 1997 we contacted Dr. Chambers to verify that he had received the desk copy of the final report for the study entitled "A randomized, double masked, parallel group, contralateral eye comparison of the bioequivalence of Bausch & Lomb Pharmaceuticals Inc. (BLP) tobramycin/dexamethasone ophthalmic suspension compared to TobraDex® ophthalmic suspension in volunteers exposed to allergen challenge." During our conversation he mentioned that he had started to review the document and had noted a potential issue with regard to itching parameter. Although this issue may be resolved upon further inspection of the data, we thought we should provide several observations/comments that demonstrate the similarity in the itching response between BLP tobramycin/dexamethasone and TobraDex®.

General Observations/ Comments:

- The itching response in the allergen challenge model is time dependent and is self-limiting over the 30 minute time period. Thus, the early observation time points (i.e., 3 and 10 minutes) are the primary focus of the itching comparisons.
- A direct comparison of itching at Visit 3 should be the primary comparison of the products.
- Itching was a secondary endpoint in the study. The study was not powered to assess itching between placebo or the two test products.
- As discussed, bioequivalence with regards to the itching parameter was determined by similarity in the responses of test products and not necessarily based on statistical evaluation.

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Received 4-16-97

Data Analyses:

- Direct comparison of the two products at Visit 3 demonstrated that the responses were not significantly different from each other (Table 15).
- Compared to contralateral placebo, Visit 3 data showed that both products produced similar responses at both the 3 and 10 minute time points following challenge (Table 22).
- The 3 and 10 minute responses were statistically different from contralateral placebo for both products (Table 22).

Thus, the Visit 3 itching data were very similar between the two products and clinically and statistically superior over placebo. Interestingly, minor difference were noted between the two products in the back to baseline analyses. However, greater variability in these analyses make the differences difficult to interpret. For example (Table 17), the absolute changes from placebo at 3 minutes was greater in the BLP group than the TobraDex® group (-0.25 vs. -0.22) although only the latter group was significantly different. Thus, while minor differences may exist, the results as a whole indicate that the BLP tobramycin/dexamethasone and TobraDex® demonstrate similar effects and are clinically bioequivalent with regards to the itching parameter.

During our telephone conversation Dr. Chambers also requested a copy of the SAS data set. This data file along with supporting documentation were sent to Dr. Chambers and the Office of Generic Drugs on April 9, 1997.

Please feel free to contact us if you have any questions regarding the study.

Sincerely,

David Mottola, PhD
Manager, Clinical Affairs
phone - 813 975-7700 ext. 7171
fax - 813 975-7721

Donald H. Chmielewski, R.Ph.
Director, Regulatory Affairs

813 975 7700
Fax 813 975 7770

NAS - assigned to Bio for review

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...Document Control Room
...Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP BIOAVAILABILITY
NC/BIO

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment

Dear Sir or Madam:

The purpose of this correspondence is to update the application with information pertinent to the bioequivalence study for the above referenced application submitted on February 14, 1997.

A discussion occurred between Dr. Wiley Chambers (FDA) and Bausch and Lomb Pharmaceuticals on April 2, 1997. During that conversation, Dr. Chambers requested a SAS data set diskette of the study. Enclosed is the data diskette and supplemental information for the data set. A copy is also being sent to Dr. Chambers' office. Questions for the statistician can be directed to Bernard Rosner, Ph.D., (617) 525-2743.

If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 or by fax at (813) 975-7757.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski, R.Ph.
Director
Regulatory Affairs

DHC

Attachments

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4/16/97

Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

April 4, 1997

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Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

BIOAVAILABILITY

Re: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment

Dear Sir or Madam:

The purpose of this correspondence is to update the application with information pertinent to the performance of the bioequivalence study for the above referenced application.

A discussion occurred between Dr. Wiley Chambers (FDA) and Bausch and Lomb Pharmaceuticals on October 16, 1996. During that conversation, agreements were made as to the design and measurement of the bioequivalence for the proposed tobramycin/dexamethasone study. A summary of the agreements was sent to Dr. Chambers for his concurrence. Unfortunately, a copy was not forwarded to the application when the meeting occurred. At this time we are providing for the record a copy of the points discussed during the telephone conference, as was provided to Dr. Chambers.

If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 or by fax at (813) 975-7757.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski, R.Ph.
Director
Regulatory Affairs

DHC

Attachments

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AADA 64-134

SEP 19 1997

5 White

Bausch & Lomb Pharmaceuticals, Inc.
Pharmaceutical Division
Attention: David Desris
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

Reference is made to the Abbreviated Antibiotic Drug Application amendment submitted on February 14, 1997, for Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. For the itching parameter, the results indicated that while the Tobradex® (reference product) demonstrates a difference from the placebo groups, the test product (BLP), does not demonstrate a consistent pattern. The study fails to demonstrate bioequivalence because of the inability to demonstrate equivalence with respect to itching.

2. The reviewing Medical Officer states, "Evidence of effectiveness and bioequivalence appears to exist with respect to the conjunctive injection parameter, but not with the itching parameter. These two signs/symptoms define the measurable allergic response in the eye and, while different pharmacologic agents have different effects on each, corticosteriods are well known to be effective in both. The clear differences seen with respect to conjunctive injection should also have been observed with itching. Although the Tobradex® performs better than the test product, it did not perform as well as expected. It is more likely that this represents a failed study than true inequivalence".

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Pharmaceutical Division | 3500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

February 14, 1997

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Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
BIOAVAILABILITY

RE: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Bioequivalence Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the agency's letter, dated June 6, 1996, for the above referenced application.

To facilitate your review, each of the observations and our corresponding response is provided below. Necessary supportive documentation is also provided for each response in the Attachments. As requested, a copy of the June 6, 1996 letter is provided in Attachment 1.

Reference is made to your observations:

Observation 1: "While differences in physical parameters have been noted, the differences are considered immaterial if clinical bioequivalence can be determined by clinical testing or by adequate comparisons of aqueous humor levels. The small number of subjects, the unexpectedly large variability, the assay reproducability and the deviation from normality are significant flaws in reported results of this study. The original protocol designed assumed normality and clinical expectations would predict normality.

The data from this study alone cannot be used to assess bioequivalence."

Response:

We agree with the noted observations regarding the bioequivalence study included with the initial AADA 64-134 Submission. Due to the difficulty with studying adequate number of patients to assess aqueous humor levels of dexamethasone after ophthalmic administration, we have abandoned this approach. However, as the agency suggested, we have conducted a clinical bioequivalence study using a well described human allergen challenge model. The protocol was discussed with Dr. Wiley Chambers, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drugs, due to his past experience with the allergen challenge model.

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The human allergen challenge study was a randomized, double-masked placebo controlled, parallel group, contralateral eye comparison to assess the clinical bioequivalence of Bausch & Lomb Pharmaceutical Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension (BLP) and TobraDex® Ophthalmic Suspension in reducing hyperemia associated with acute allergic conjunctivitis induced by topical allergen challenge.

The study consisted of three visits; Visit 1 (Day 0), Visit 2 (Day 19) and Visit 3 (Day 21). During Visit 1 and Visit 2 the subjects were challenged with an allergen to determine a consistent conjunctival hypermia response. On Visit 3 subjects randomly received 2 drops of BLP product or TobraDex® in one eye and placebo in the contralateral eye. Each subject received an allergen challenge at 3 and 6 hours after administration of the study drug. Symptoms of allergic conjunctivitis were assessed at 3, 10, 20, and 30 minutes after each allergen challenge.

Briefly, the results demonstrated clinical bioequivalence between BLP product and TobraDex® and are summarized below:

- BLP product and TobraDex® produced conjunctival hyperemia responses on Visit 3 that were not statistically different (primary efficacy analysis).
- BLP product and TobraDex® both reduced hyperemia scores by greater than 1 unit compared to baseline (i.e., a 40-50% decrease from baseline scores).
- BLP product and TobraDex® both produced a statistically significant ($p \leq 0.0005$) reduction in hyperemia compared to placebo (≈ 0.5 unit). This change equates to approximately a 20% absolute and 45% relative reduction from placebo scores.
- BLP product and TobraDex® both produced similar responses on the other signs and symptoms of allergic conjunctivitis, notably average hyperemia (average of all three vessel beds) and itching.
- BLP product and TobraDex® produced conjunctival hyperemia responses on Visit 3 that were supportive of equivalence based on traditional (pharmacokinetic) bioequivalence statistical criteria.
- Within subject population analyses (correlated proportions) demonstrated that in those subjects that discriminated a defined response (i.e., Visit 3 score ≤ 1 or back to baseline change ≥ 1 unit), there was a statistically significant greater response to BLP product and TobraDex® treatment compared to placebo.

These results clearly demonstrate the corticosteriod activity of BLP and TobraDex® are clinically bioequivalent. The complete final study report is included in Attachment 2 entitled:

"A randomized, double-masked, parallel group, contralateral eye comparison of the clinical bioequivalence of Bausch & Lomb Pharmaceuticals Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension compared to TobraDex® Ophthalmic Suspension in volunteers exposed to allergen challenge"

Observation 2: "There is a clear misunderstanding of testing methodology. The test performed provides no useful information concerning the effect of this particular formulation on the killing rate of the microorganisms listed for the product.

The in vitro "kill rate" should be performed in studies comparing Tobradex® to the proposed tobramycin-dexamethasone formulation.

Each formulation should be challenged with approximately $5x10^4$ CFU/mL of each of the following panel of microorganisms in order to compare their antibacterial kill rates:

1. ***All organisms listed in the USP Preservative effectiveness test.***

2. ***All organisms listed in the Indications section of the labeling for Tobradex®.***

The inoculated product samples should be quantified for surviving viable bacteria (in CFU/mL) after 30, 60, 120, 240 and 360 minutes of contact time. The testings should be performed at least twice.

Response:

We have conducted a comprehensive evaluation of the *in vitro* "kill rate" of Bausch & Lomb Pharmaceuticals Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension (BLP) compared to TobraDex®. The study followed the agency's recommendations as stated above and additional discussions (November 20, 1996) with the Office of Bioequivalence which requested that bacterial cultures should be tested at the same inoculum level but at 5, 15, 30, 60 and 120 minutes.

Briefly, the results demonstrated that BLP and TobraDex® had equivalent antimicrobial activity over time for all organisms contained in the USP Preservative Effectiveness Test and the TobraDex® package insert. All of the tested bacteria were "killed" at the 5 minute assessment time (0% growth). BLP product and TobraDex® had equivalent "kill rates" for *Candida albicans* (yeast) and *Aspergillis niger* (mold).

Therefore, the tobramycin (antimicrobial) activity of the BLP product and TobraDex® are equivalent. The complete final study report is included in Attachment 3 entitled:

> "Comparison of *In-Vitro* microbial kill rates: TobraDex® and Bausch & Lomb Pharmaceuticals Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension."

Summary:

The results from the clinical bioequivalence study and the *in vitro* "kill rate" study demonstrate that the corticosteroid and tobramycin activity of BLP and TobraDex® are equivalent.

We believe this correspondence provides a thorough response to the questions raised in the agency's June 6, 1996 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above referenced address or by telephone at (813) 975-7775 or by fax at (813) 975-7757.

Sincerely,

David Desris

David Desris, R.Ph.
Manager
Regulatory Affairs

DD/bab

Attachments

Pharmaceutical Division | 3500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

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December 4, 1996

AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD & DRUG ADMINISTRATION
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
DEC 0 5 1996

RE: AADA 64-134
Tobramycin & Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Telephone Amendment

Dear Sir or Madam:

This correspondence is in response to your November 27, 1996 phone comment concerning Part C, Observaton 2 of our June 11,1996 submission regarding process validation data for Filling Line #2.

The most recent media fill data that we have for the smallest container/closure system is for the 5.75ml container with a 2ml fill volume (filled 6-18-93) and the largest is a 15ml container with a 7.6ml fill volume (filled 4-16-96), as noted in the table below. Media fill requalification of employs the container designated as "worst case", which is the largest container/closure system (15ml/15mm). The smallest container/closure media fill qualification is generally only completed in the initial qualification of a media fill line and not for the requalifications.

Date Filled	Lot Number	Units Filled	Duration of Run	No.of Operators	Contamination Rate	Number of Positives	Container/ Closure	Fill Volume
6/18/93	423541		s		0.00%	0	5.75ml/13mm	2ml
4/16/96	773471		rs		0.00%	0	15ml/15mm	7.6ml

After you have reviewed the enclosed information, if you have any questions/ comments or need additional information or clarification, please contact me at the above address or by phone at (813) 975-7775.

Sincerely,

David Desris

David Desris R.Ph.
Manager
Regulatory Affairs

enclosure

LETTER SENT 9/5/96

Bausch & Lomb Pharmaceuticals, Inc.
Pharmaceutical Division
Attention: Cal Bowman
8500 Hidden River Parkway
Tampa, FL 33637

Reference Number: P 96-054

Dear Mr. Bowman:

Reference is made to the proposed bioequivalence study protocol (No 9608) and meeting request submitted for review August 19, 1996 to the Office of Generic Drugs for Tobramycin and Dexamethasone Ophthalmic Suspension USP.

The Office of Generic drugs has reviewed the correspondence and the following comments are provided for you consideration:

1. The Office normally reserves meetings to discuss complex scientific issues that are not readily resolved through correspondence. Further the Office has a review process for proposed bioequivalence study protocols. Given these considerations the Office would like to postpone granting the meeting until the Office has reviewed the submitted protocol and provided you with our comments. If after reviewing our comments you conclude a meeting is still warranted please let us know and we will consider your request at that time.

2. The Office has assigned a control number of P 96-054 to this protocol and excepts to have the review completed in approximately 120 days. If you have any questions please feel free to call and reference the appropriate control number.

If you have any questions, either about this letter, or, in reference to the proper procedures to follow to finalize a meeting, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

Pharmaceutical Division 8500 Hidden River Parkway Tampa FL 33637 813 975 7775 Fax 813 975 7757

Clawson C. Bowman, J.D.
Vice President
Regulatory Affairs

BAUSCH & LOMB
Healthcare and Optics Worldwide

August 19, 1996

BIOAVAILABILITY

NEW CORRESP

Keith K. Chan, Ph.D.
Division Director of Bioequivalence
CDER
Food and Drug Administration
Metro Park North 2
7500 Standish Place, HFD-650
Rockville, MD 20855

Dear Dr. Chan:

/ and I would like to thank you for the time you spent with us at the RAPS Drug Briefing. We are especially grateful that you said you would meet with us to discuss our recent bioequivalence deficiency letter on our Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1% AADA submission.

FDA's deficiency letter (attached) contains two main points. We would like to discuss the first point with you. The second point is clear and we have already begun taking the appropriate steps to address this issue.

We recognize that several approaches could be taken to address item one. Our initial reaction was to provide FDA information that establishes the variability found in our study to be within the expected range. However, after further discussions with experts in the field and with Dr. Wiley Chambers, we believe we have developed a better approach which we would like to discuss with you.

We are aware that you and your department will be spending a great deal of time and effort preparing for the FDA / Industry Meeting on Bioequivalence issues scheduled for the first week in September. Therefore, we suggest that a meeting be scheduled for the following week. Naturally, we will arrange our schedules to meet with you any time during that week that you are available. We believe the meeting should take approximately one hour.

The agenda for the meeting will be a detailed discussion of the first point in the deficiency letter and then a discussion of our proposed approach to providing us (FDA and BLP) more meaningful information.

I will telephone you next week to learn the exact time and date for the meeting.

Sincerely,

Cal Bowman

Cal Bowman
VP, Regulatory Affairs
Bausch & Lomb Pharmaceuticals (BLP)

RECEIVED
SEP 0 5 1996
GENERIC DRUGS

Pharmaceutical Division | 3500 Mason River Parkway, Tampa FL 33637 | 813 975 7760 Fax 813 975 7770

June 11, 1996

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3% / 0.1%
Major Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the agency's "Not Approvable" letter, dated March 12, 1996, for the above referenced application. In that letter the agency stated that this response would be considered a major amendment.

To facilitate your review, each of the observations and our corresponding response is provided as an attachment to this amendment. Necessary supportive documentation is also provided for each response.

We would like to take this opportunity to amend the application beyond the scope of the agency's observations. Specifically, we wish to revise the osmolality specifications related to in-process and product release criteria. The new specifications will provide criteria that better compliment the values measured for the exhibit batch. A data table, which includes both the current specifications, revised specifications and a summary of the related exhibit batch data submitted previously is provided under Attachment C.

We believe this correspondence provides a thorough response to the questions raised in the agency's March 12, 1996 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

Sincerely,

Peter Stoelzle
Director
Regulatory Affairs

enclosure

November 17, 1995
Gratuitous Amendment
AADA 64-134

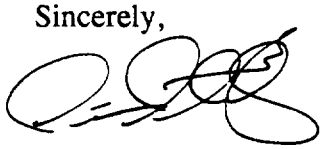
We believe this correspondence compounded with our August 31, 1995 response letter would satisfy any issues on chromatographic impurity levels for Bausch & Lomb's pending application.

In accordance with 21 CFR 314.96(b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have questions regarding this amendment, please contact me at the above address or by phone at (813) 975-7775.

Sincerely,



Peter Stoelzle
Director
Regulatory Affairs

enclosure

November 17, 1995

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20857

RE: Gratuitous Amendment
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%
AADA 64-134

The purpose of this correspondence is to amend the above referenced abbreviated new drug application. Specifically, we wish to provide additional information to substantiate the comparable impurity profiles of our proposed formula and that of the reference listed drug product (RLD).

In an earlier amendment, dated August 31, 1995, we provided information which compared impurity profiles between the RLD and Bausch & Lomb drug product (BLP). On page 1016 of that correspondence, we indicated that the USP reference standard and BLP exhibit batch included two late eluting impurities not found in the sole RLD lot originally evaluated. We indicated it was likely these impurities would appear in RLD product lots, given that the USP reference standard most often represent the active drug substance used by the innovator firm in producing their product.

We have since evaluated additional commercially available lots of the RLD for both TobreDex® Ophthalmic Suspension and Tobrex® Ophthalmic Solution. Their chromatographic impurities results are presented in Attachment 1 and verifies the drug products currently represented in the market contain similar chromatographic impurity profiles as that represented by Bausch & Lomb's drug product, including the late eluting peaks referenced earlier. Since each of these drug products are the subject of an approved new drug application, drug product quality and safety issues concerning the levels of impurities have been successfully satisfied.

We feel substantial evidence has already been provided in the August 31, 1995 response concerning impurity profiles. However, this additional information provides further verification that the quality and thus, impurity profiles for Tobramycin based products across dosage forms, is indicative of the comparable quality of the drug product pending within this application.

AADA 64-134

JUN -6 1996

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Peter Stoelze
8500 Hidden River Parkway
Tampa FL 33637

Dear Sir:

Reference is made to the Antibiotic Drug Application submitted on August 31, 1995, for Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%.

The Office of Generic Drugs in consultation with Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. While differences in physical parameters have been noted, the differences are considered immaterial if clinical bioequivalence can be determined by clinical testing or by adequate comparisons of aqueous humor levels. The small number of subjects, the unexpectedly large variability, the assay reproducability and the deviation from normality are significant flaws in reported results of this study. The original protocol designed assumed normality and clinical expectations would predict normality.

   The data from this study alone cannot be used to assess bioequivalence.

2. There is a clear misunderstanding of testing methodology. The test performed provides no useful information concerning the effect of this particular formulation on the killing rate of the microorganisms listed for the product.

   The *in vitro* "kill rate" should be performed in studies comparing Tobradex® to the proposed tobramycin-dexamethasone formulation.

   Each formulation should be challenged with approximately $5x10^4$ CFU/mL of each of the following panel of microorganisms in order to compare their antibacterial kill rates:

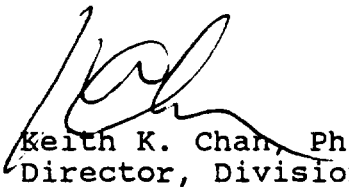
   1. All organisms listed in the USP Preservative effectiveness test.

2. All organisms listed in the Indications section of the labeling for Tobradex ®.

   The inoculated product samples should be quantified for surviving viable bacteria (in CFU/mL) after 30, 60, 120, 240 and 360 minutes of contact time. The testings should be performed at least twice.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,



Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Pharmaceutical Division
Tampa FL 33637
Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

September 21, 1994

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: AADA 64-134
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%
Response to the agency's "Refuse to File" letter dated August 22, 1994

Dear Sir or Madam:

This correspondence is in response to the agency's August 22, 1994 "refuse to file" letter for the above referenced application. In that letter the agency noted that an in vivo bioequivalence study is required as part of the submission.

As a result, we have been working with industry experts and health care practitioners over the past several weeks to develop an appropriate study. We will request a meeting with the Bioequivalence group within the next week to discuss our proposed study protocol.

We expect to amend the application during January, 1995 to include data from studies, the protocols of which have been agreed to by the agency and which satisfy the agency's bioequivalence requirements. Any revision to that timeframe will be reported to the agency.

In accordance with Federal Register, Vol. 58. No. 172 (Effective October 8, 1993), we certify that a true copy of this correspondence has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this communication, please contact me at the above address or by phone at (813) 975-7775.

Sincerely,

for

Peter Stoelzle
Director
Regulatory Affairs

Pharmaceutical Division
Tampa FL 33637

BAUSCH & LOMB
Healthcare and Optics Worldwide

July 29, 1994

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD 600
5600 Fisher Lane
Rockville, MD 20857

RE: Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1% (Sterile)
AADA Submission

Dear Sir or Madam:

In accordance with the provisions set forth in Section 507 of the Federal Food, Drug and Cosmetic Act, we are submitting this abbreviated antibiotic drug application, in duplicate, for Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1% (Sterile). This product is indicated for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Standard operating procedures (SOPs) are provided throughout this application as an aid in the review process. Revisions may be made to these SOPs after appropriate in-house review and approval.

In accordance with Federal Register, Vol. 58, No. 172 (Effective October 8, 1993), we certify that a true copy has been sent to our FDA district office in Orlando,Florida.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions or comments concerning this application, please contact me at the above address or at (813) 975-7775.

Sincerely,

Peter Stoelzle
Director
Regulatory Affairs

Enclosures

AADA 64-134

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Peter Stoelzle
8500 Hidden River Parkway
Tampa, FL 33637

MAR 12 1996

Dear Sir:

This is in reference to your abbreviated antibiotic application dated July 29, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%.

Reference is also made to your amendments dated August 31 and November 17, 1995.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

A. Chemistry Deficiencies:

1.

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

7/29/94

5.

batch sheet.

B. Labeling Deficiencies:

1. GENERAL COMMENTS:

Your proposed proprietary name, T-DEX has been submitted to the CDER Labeling and Nomenclature Committee and has been found unacceptable for the following reason:

A review revealed one name which sounds like and looks like your proposed proprietary name: Tidex (Dextroamphetamine Sulfate Tablets by Allison). The Committee believes the two names are sufficiently close to find the proposed name misleading as defined in 21 CFR 201.10(c)(5).

Delete T-DEX from all labels and labeling and/or propose another proprietary name for our review and comment prior to submitting final printed labeling.

2. CONTAINER: 2.5 mL and 5 mL

   Please ensure the following text appears on the label:

   PRECAUTIONS: Do not touch dropper tip to any surface, as this may contaminate the suspension. FOR TOPICAL EYE USE ONLY

3. CARTON: 2.5 mL and 5 mL

   We encourage you to add "FOR TOPICAL EYE USE ONLY"

4. INSERT

   a. GENERAL COMMENT

      Please note, if a proprietary name appears in a column of running text, then the established name shall appear at least once in association with the proprietary name. We refer you to 21 CFR 210.10 (g)(1)) for guidance. Revise your insert accordingly.

   b. CLINICAL PHARMACOLOGY

      Delete the sentence "A significant bacterial...prolonged use." from the sixth paragraph.

   c. CONTRAINDICATIONS

      Delete the second paragraph "The use...body."

   d. PRECAUTIONS

      i. General - Add the following text as the second paragraph.

         Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

ii. Information for Patients - "...dropper tip to any..."

iii. Pediatric Use - "...in pediatric patients have..."

e. Include the following section so that it follows the ADVERSE REACTIONS section.

OVERDOSAGE:

Clinically apparent signs and symptoms of an overdosage of tobramycin and dexamethasone ophthalmic suspension(punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

Please revise your labels and labeling, as instructed above, and if you choose to propose another trade name, submit draft, otherwise, submit final printed labels and labeling. Please note we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

C. Microbiology Deficiencies

1. Although the validation runs provided for the sterilization specified no actual cycle specifications were found. Please specify the cycles with respect to concentration, exposure time , holding time and aeration time for the components used in this drug product and for the relevant validation cycles.

2. Please provide more recent process validation data for The data should contain containers and fill volumes which are more representative of this drug product.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

3/11/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research