CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076622

Name: Ofloxacin Ophthalmic Solution 0.3%

Sponsor: Bausch & Lomb, Inc.

Approval Date: May 14, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

APPROVAL LETTER

ANDA 76-622

MAY 14 2004

Bausch & Lomb, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ofloxacin Ophthalmic Solution USP, 0.3%.

Reference is also made to our Tentative Approval letter dated January 23, 2004, and to your amendments dated March 12, March 16, and April 22, 2004.

We have completed the review of this tentatively approved abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ofloxacin Ophthalmic Solution USP, 0.3%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ocuflox® Ophthalmic Solution, 0.3%, of Allergan, Inc.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 5/14/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-622
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-629/G.Kang/GK 5/3/04
HFD-623/J.Fan/ 5/4/04
HFD-617/T.Vu/ 5/4/04
HFD-613/B.Weitzman/BW 5/5/04
HFD-613/J.Grace/ 5/5/04
HFD-600/N.Nath/ 5/4/04
HFD-600/N.Sweeney/ N. Sweeney 5-4-04

Robert West
5/6/2004
Pending expiration of Allergan's exclusivity ('456 patent).

AS
RWest
5/5/04

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F/T by

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

TENTATIVE APPROVAL LETTER

ANDA 76-622

JAN 23 2004

Bausch & Lomb, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ofloxacin Ophthalmic Solution USP, 0.3%.

Reference is also made to your amendments dated June 16, November 11, (2 submissions), and December 31, 2003.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval at this time because of the listed patents and their associated market exclusivity as noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product, (Ocuflox® Ophthalmic Solution, 0.3% by Allergan, Inc.), upon which you have based your application is currently subject to periods of marketing exclusivity. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 4,382,892 (the '892 patent) and U.S. patent 4,551,456 (the '456 patent) were to have expired on September 2, 2003, and November 14, 2003, respectively. Your application contains paragraph II certifications to each of these patents under Section 505(j)(21)(A)(vii)(II) of the Act. However, the expiration of each patent has effectively been

extended by an additional 6 months of marketing exclusivity under Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The Modernization Act created Section 505(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505(A) permits certain applications to obtain an additional six months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the NDA sponsor submits requested information relating to the use of ofloxacin ophthalmic solution in the pediatric population. Allergan Inc. (Allergan) has submitted such information to the agency. The agency has determined that this information meets the criteria stated in the statute and has granted Allergan 6 months of additional marketing exclusivity with respect to each of the listed patents for Ocuflox Ophthalmic Solution, 0.3%. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the latter of the periods of market exclusivity has expired, i.e., May 14, 2004. The final approval date may be further extended if upon review of the pediatric data submitted by Allergan the agency decides that Allergan is eligible for an additional period of Hatch-Waxman exclusivity.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 60 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the ANDA and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may also lead to a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to May 14, 2004, you should amend your application accordingly.

For further information on the status of this application, and prior to your submission of the minor amendment referenced above, please contact Thuyanh Vu, Project Manager, at 301-827-5754, for further instructions.

Sincerely yours,

Gary Buehler 1/23/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-622
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-629/G.Kang/ GK 1/20/04
HFD-623/J.Fan/ 1/20/04
HFD-617/T.Vu/
HFD-600/N.Nath/ 1/20/04
HFD-600/N.Sweeney/ N. Sweeney 1-21-04
HFD-613/B.Weitzman/ BW 1/21/2004
HFD-613/J.Grace/ 1/21/2004

Robert West 1/23/2004

RLWest 1/21/04

F/T by

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

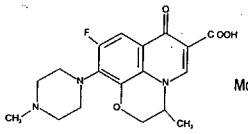
ANDA 076622

LABELING

Ofloxacin
Ophthalmic Solution 0.3%

Rx only STERILE

DESCRIPTION:
Ofloxacin Ophthalmic Solution 0.3% is a sterile ophthalmic solution. It is a fluorinated carboxyquinolone anti-infective for topical ophthalmic use.



$C_{18}H_{20}FN_3O_4$ Mol. Wt. 361.37

Chemical Name:
(±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid.

Each mL Contains: Active:
ofloxacin 0.3% (3 mg/mL)

Preservative Added:
benzalkonium chloride (0.005%)

Inactives: sodium chloride and purified water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH. Ofloxacin ophthalmic solution is unbuffered and formulated with a pH of 6.4 (range - 6.0 to 6.8). It has an osmolality of 300 mOsm/kg. Ofloxacin is a fluorinated 4-quinolone which differs from other fluorinated 4-quinolones in that there is a six member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.

CLINICAL PHARMACOLOGY:
Pharmacokinetics: Serum, urine and tear concentrations of ofloxacin were measured in 30 healthy women at various time points during a ten-day course of treatment with ofloxacin ophthalmic solution. The mean serum ofloxacin concentration ranged from 0.4 ng/mL to 1.9 ng/mL. Maximum ofloxacin concentration increased from 1.1 ng/mL on day one to 1.9 ng/mL on day 11 after QID dosing for 10 1/2 days. Maximum serum ofloxacin concentrations after ten days of topical ophthalmic dosing were more than 1000 times lower than those reported after standard oral doses of ofloxacin.

Tear ofloxacin concentrations ranged from 5.7 to 31 µg/g during the 40 minute period following the last dose on day 11. Mean tear concentration measured four hours after topical ophthalmic dosing was 9.2 µg/g.

Corneal tissue concentrations of 4.4 µg/mL were observed four hours after beginning topical ocular application of two drops of ofloxacin ophthalmic solution every 30 minutes. Ofloxacin was excreted in the urine primarily unmodified.

Microbiology: Ofloxacin has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria. Ofloxacin is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Ofloxacin is thought to exert a bactericidal effect on susceptible bacterial cells by inhibiting DNA gyrase, an essential bacterial enzyme which is a critical catalyst in the duplication, transcription, and repair of bacterial DNA.

Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides. Ofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and clinically, in conjunctival and/or corneal ulcer infections as described in the **INDICATIONS AND USAGE** section.

AEROBES, GRAM-POSITIVE:
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*

ANAEROBIC SPECIES:
- *Propionibacterium acnes*

AEROBES, GRAM-NEGATIVE:
- *Enterobacter cloacae*
- *Haemophilus influenzae*
- *Proteus mirablis*
- *Pseudomonas aeruginosa*
- *Serratia marcescens**

*Efficacy for this organism was studied in fewer than 10 infections

The safety and effectiveness of ofloxacin ophthalmic solution in treating ophthalmologic infections due to the following organisms have not been established in adequate and well-controlled clinical trials. Ofloxacin ophthalmic solution has been shown to be active *in vitro* against most strains of these organisms but the clinical significance in ophthalmologic infections is unknown.

AEROBES, GRAM-POSITIVE:
- *Enterococcus faecalis*
- *Listeria monocytogenes*
- *Staphylococcus capitis*
- *Staphylococcus hominus*
- *Staphylococcus simulans*
- *Streptococcus pyogenes*

AEROBES, GRAM-NEGATIVE:
- *Acinetobacter calcoaceticus var. anitratus*
- *Acinetobacter calcoaceticus var. lwoffi*
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Enterobacter aerogenes*
- *Enterobacter agglomerans*
- *Escherichia coli*
- *Haemophilus parainfluenzae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Moraxella (Branhamella) catarrhalis*
- *Moraxella lacunata*
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Pseudomonas acidovorans*
- *Pseudomonas fluorescens*
- *Shigella sonnei*

OTHER:
- *Chlamydia trachomatis*

Clinical Studies:
Conjunctivitis: In a randomized, double-masked, multicenter clinical trial, ofloxacin ophthalmic solution was superior to its vehicle after 2 days of treatment in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated a clinical improvement rate of 86% (54/63) for the ofloxacin treated group versus 72% (48/67) for the placebo treated group after 2 days of therapy. Microbiological outcomes for the same clinical trial demonstrated an eradication rate for causative pathogens of 65% (41/63) for the ofloxacin treated group versus 25% (17/67) for the vehicle treated group after 2 days of therapy. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

Corneal Ulcers: In a randomized, double-masked, multi-center clinical trial of 140 subjects with positive cultures, ofloxacin ophthalmic solution treated subjects had an overall clinical success rate (complete re-epithelialization and no progression of the infiltrate for two consecutive visits) of 82% (61/74) compared to 80% (53/66) for the fortified antibiotic group, consisting of 1.5% tobramycin and 10% cefazolin solutions. The median time to clinical success was 11 days for the ofloxacin treated group and 10 days for the fortified treatment group.

INDICATIONS AND USAGE:
Ofloxacin ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the following bacteria in the conditions listed below:

CONJUNCTIVITIS:
Gram-positive bacteria:
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*

Gram-negative bacteria:
- *Enterobacter cloacae*
- *Haemophilus influenzae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

CORNEAL ULCERS:
Gram-positive bacteria:
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*

Gram-negative bacteria:
- *Pseudomonas aeruginosa*
- *Serratia marcescens**

Anaerobic species:
- *Propionibacterium acnes*

*Efficacy for this organism was studied in fewer than 10 infections

CONTRAINDICATIONS
Ofloxacin ophthalmic solution is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS
NOT FOR INJECTION.
Ofloxacin ophthalmic solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. A rare occurrence of Stevens-Johnson syndrome, which progressed to toxic epidermal necrolysis, has been reported in a patient who was receiving topical ophthalmic ofloxacin. If an allergic reaction to ofloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation should be administered as clinically indicated.

PRECAUTIONS
General: As with other anti-infectives, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. Ofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

The systemic administration of quinolones, including ofloxacin, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Ofloxacin, administered systemically at 10 mg/kg/day in young dogs (equivalent to 110 times the maximum recommended daily adult ophthalmic dose) has been associated with these types of effects.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Drug Interactions: Specific drug interaction studies have not been conducted with ofloxacin ophthalmic solution. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames test, *in vitro* and *in vivo* cytogenic assay, sister chromatid exchange assay (Chinese hamster and human cell lines), unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocyte, and in the mouse lymphoma assay.

In fertility studies in rats, ofloxacin did not affect male or female fertility or morphological or reproductive performance at oral dosing up to 360 mg/kg/day (equivalent to 4000 times the maximum recommended daily ophthalmic dose).

Pregnancy: Teratogenic Effects. Pregnancy Category C: Ofloxacin has been shown to have an embryocidal effect in rats and in rabbits when given in doses of 810 mg/kg/day (equivalent to 9000 times the maximum recommended daily ophthalmic dose) and 160 mg/kg/day (equivalent to 1800 times the maximum recommended daily ophthalmic dose). These dosages resulted in decreased fetal body weight and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Nonteratogenic Effects: Additional studies in rats with doses up to 360 mg/kg/day during late gestation showed no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn.

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In nursing women a single 200 mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical ophthalmic administration. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in infants below the age of one year have not been established.

Quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after oral administration; however, topical ocular administration of ofloxacin to immature animals has not shown any arthropathy. There is no evidence that the ophthalmic dosage form of ofloxacin has any effect on weight bearing joints.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS:
Ophthalmic Use: The most frequently reported drug-related adverse reaction was transient ocular burning or discomfort. Other reported reactions include stinging, redness, itching, chemical conjunctivitis/keratitis, ocular/periocular/facial edema, foreign body sensation, photophobia, blurred vision, tearing, dryness, and eye pain. Rare reports of dizziness and nausea have been received.

DOSAGE AND ADMINISTRATION:
The recommended dosage regimen for the treatment of **bacterial conjunctivitis** is:

Days 1 and 2	Instill one to two drops every two to four hours in the affected eye(s).
Days 3 through 7	Instill one to two drops four times daily.

The recommended dosage regimen for the treatment of **bacterial corneal ulcer** is:

Days 1 and 2	Instill one to two drops into the affected eye every 30 minutes, while awake. Awaken at approximately four and six hours after retiring and instill one to two drops.
Days 3 through 7 to 9	Instill one to two drops hourly, while awake.
Days 7 to 9 through treatment completion	Instill one to two drops, four times daily.

DO NOT USE IF IMPRINTED "Protective Seal" WITH YELLOW IS NOT INTACT.

HOW SUPPLIED;
Ofloxacin Ophthalmic Solution 0.3% is supplied sterile in plastic dropper bottles in the following sizes:

5 mL	NDC 24208-434-05	AB43407
10 mL	NDC 24208-434-10	AB43409

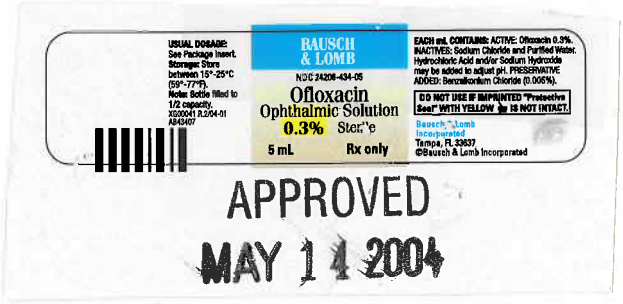
Storage: Store at 15°-25°C (59°-77°F)

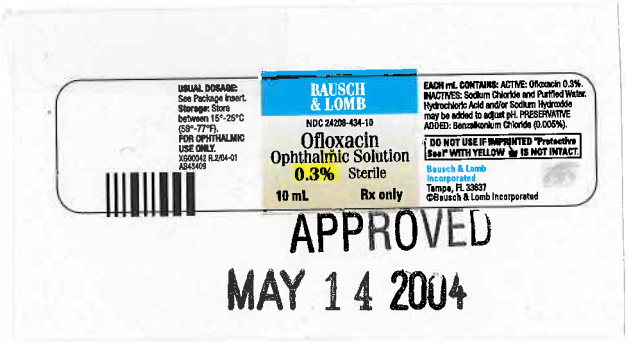
KEEP OUT OF REACH OF CHILDREN.

FOR OPHTHALMIC USE ONLY.

Bausch & Lomb Incorporated
Tampa, FL 33637

X051054 **(FOLDED)**
XM10124 **(FLAT)**
R.2/04-01


USUAL DOSAGE:
See Package Insert.
Storage: Store between 15°-25°C (59°-77°F).
Note: Bottle filled to 1/2 capacity.
XG00041 R.2/04-01
AB45407
BAUSCH & LOMB
NDC 24208-434-05
Ofloxacin
Ophthalmic Solution
0.3% Sterile
5 mL Rx only
EACH mL CONTAINS: ACTIVE: Ofloxacin 0.3%. INACTIVES: Sodium Chloride and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH. PRESERVATIVE ADDED: Benzalkonium Chloride (0.005%).
DO NOT USE IF IMPRINTED "Protective Seal" WITH YELLOW IS NOT INTACT.
Bausch & Lomb Incorporated
Tampa, FL 33637
©Bausch & Lomb Incorporated
APPROVED
MAY 14 2004


USUAL DOSAGE:
See Package Insert.
Storage: Store between 15°-25°C (59°-77°F).
FOR OPHTHALMIC USE ONLY.
XG00042 R.2/04-01
AB45408
BAUSCH & LOMB
NDC 24208-434-10
Ofloxacin
Ophthalmic Solution
0.3% Sterile
10 mL Rx only
EACH mL CONTAINS: ACTIVE: Ofloxacin 0.3%. INACTIVES: Sodium Chloride and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH. PRESERVATIVE ADDED: Benzalkonium Chloride (0.005%).
DO NOT USE IF IMPRINTED "Protective Seal" WITH YELLOW IS NOT INTACT.
Bausch & Lomb Incorporated
Tampa, FL 33637
©Bausch & Lomb Incorporated
APPROVED
MAY 14 2004

Ofloxacin Ophthalmic Solution 0.3% Sterile

EACH mL CONTAINS:
ACTIVE:
Ofloxacin 0.3%.
INACTIVES:
Sodium Chloride and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH.
PRESERVATIVE ADDED:
Benzalkonium Chloride (0.005%).

USUAL DOSAGE:
See Package Insert.

APPROVED
MAY 14 2004

Bausch & Lomb Incorporated
Tampa, FL 33637

FOR OPHTHALMIC USE ONLY.

KEEP OUT OF REACH OF CHILDREN.

Storage:
Store between 15°-25°C (59°-77°F).

Note: Bottle filled to 1/2 capacity.

DO NOT USE IF IMPRINTED "Protective Seal" WITH YELLOW IS NOT INTACT.

BAUSCH & LOMB

NDC 24208-434-05

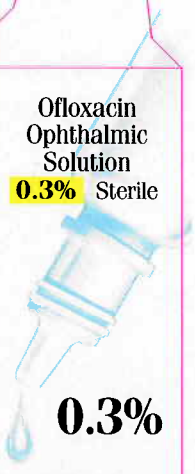
Ofloxacin Ophthalmic Solution 0.3%

STERILE

Rx only

5 mL

Ofloxacin Ophthalmic Solution 0.3% Sterile



0.3%

N 3 24208-434-05 5

XQ00120
R.2/04-01
AB43407

Ofloxacin
Ophthalmic
Solution
0.3% Sterile

EACH mL CONTAINS:
ACTIVE:
Ofloxacin 0.3%.
INACTIVES:
Sodium Chloride and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH.
PRESERVATIVE ADDED:
Benzalkonium Chloride (0.005%).

USUAL DOSAGE:
See Package Insert.

Bausch & Lomb Incorporated
Tampa, FL 33637

FOR OPHTHALMIC USE ONLY.

KEEP OUT OF REACH OF CHILDREN.

Storage:
Store between 15°-25°C (59°-77°F).

DO NOT USE IF IMPRINTED "Protective Seal" WITH YELLOW IS NOT INTACT.

BAUSCH & LOMB

NDC 24208-434-10

Ofloxacin Ophthalmic Solution 0.3%

STERILE

Rx only

10 mL

APPROVED
MAY 14 2004

Ofloxacin
Ophthalmic
Solution
0.3% Sterile

0.3%

N 3 24208-434-10 9

XQ00121
R.2/04-01
AB43409

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-622

Date of Submission: December 31, 2002

Applicant's Name:.Bausch & Lomb

Established Name: Ofloxacin Ophthalmic Solution USP, 0.3%

Labeling Deficiencies:

1. **CONTAINER**

   Satisfactory in draft.

2. **CARTON** (5 ml and 10 ml)

   Satisfactory in draft.

3. **INSERT**

   Please correct the spelling of "Iwofil" to read "Iwoffi"

Please revise your labels and labeling, as instructed above, and submit 12 final printed copies for approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

The firm did not include the 5 ml bottle size in the packaging component section, (Vol. 1.2 section XII, page 459). 10 ml bottle is used for both 5 and 10 ml fill sizes.

Qiu Kang
6/24/03

FOR THE RECORD:

1. **MODEL LABELING**
   This review was based on the labeling for Occuflox by Allergan Inc.; NDA 19-921/S008; Revised November 2000; Approved November 9, 1999.

2. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
   [Vol. A1.1 pg. 82]

2. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 19-921

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382892	Sep 02, 2003			III	None
4551456	Nov 14, 2003	U-80	METHOD OF TREATING OCULAR BACTERIAL INFECTIONS	III	NONE

Exclusivity-Data – NDA 19-921

Code	Reference	Expiration	Labeling Impact
ODE	ORPHAN DRUG EXCLUSIVITY	May 22, 2003	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers at controlled room temperature.
- RLD: Stored at 15° to 25°C (59° to 77°F).
- ANDA: Store at 15° to 25°C (59° to 77°F).

5. DISPENSING STATEMENT COMPARISON

- USP: None.
- RLD: None.
- ANDA: None.

6. PACKAGE CONFIGURATION

- RLD: Packaged in 1 ml, 5 ml, and 10 ml plastic dropper bottles with a tan cap.
- ANDA: Packaged in 5 ml, and 10 ml plastic dropper bottles with a beige cap.

7. CONTAINER/CLOSURE

Packaged into White Round 10 cc Bottles with white, extended control dropper tip and (b) (4) cap.

Please note, the packaging component section does not include the 5ml packaging components.

8. FINISHED DOSAGE FORM

- RLD: Supplied as a 1 ml, 5 ml and 10 ml
- ANDA: A clear, (b) (4) solution supplied as 5 ml and 10 ml bottles.

[Vol.1.2, pages 610 and 612]

9. CAP COLOR

- RLD: Tan color cap
- ANDA Beige color cap (Vol. 1.2, page 571)

10. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Bausch & Lomb Pharmaceuticals, Inc.
Hidden River Maufacturing Facility
8500 Hidden River Parkway
Tampa, Florida 33637
[Vol. A1.1 pg. 186]

Date of Review: **Date of Submission:** December 30, 2002

Primary Reviewer: Beverly Weitzman **Date:** 5/27/2003

B Weitzman

Team Leader: John J Grace **Date:** 5/28/2003

cc:

ANDA 76-622
DUP/DIVISION FILE
HFD-613/Jgrace (no cc) .
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Review

TENATIVE APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-622

Date of Submission: June 16, 2003

Applicant's Name: Bausch & Lomb

Established Name: Ofloxacin Ophthalmic Solution USP, 0.3%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No
Container Labels: (5 mL and 10 mL) – Satisfactory in **DRAFT** as of December 31,2002 submission [Vol 1.1]
Carton Labeling: (5 mL and 10 mL) – Satisfactory in **DRAFT** as of December 31,2002 submission [Vol 1.1]
Professional Package Insert Labeling: Satisfactory in final printed labeling as of June 16, 2003 submission. [Vol 2.1; Revised 06/03 ; Code # X051054 (folded); XM10124 (flat)]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Ocuflox Ophthalmic Solution, 0.3%
- NDA Number: 19-921/S008
- NDA Drug Name: Ofloxacin Ophthalmic Solution, 0.3%
- NDA Firm: Allergan Inc
- Date of Approval of NDA Insert: Approved November 9, 1999
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 19-921

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382892	Sep 02, 2003			III	None
4551456	Nov 14, 2003	U-80	METHOD OF TREATING OCULAR BACTERIAL INFECTIONS	III	NONE

Exclusivity Data– NDA 19-921

Code	Reference	Expiration	Labeling Impact
ODE	ORPHAN DRUG EXCLUSIVITY	May 22, 2003	NONE

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

The firm did not include the 5 ml bottle size in the packaging component section, (Vol. 1.2 section XII, page 459).

FOR THE RECORD:

1. **MODEL LABELING**
   This review was based on the labeling for Occuflox by Allergan Inc.; NDA 19-921/S008; Revised November 2000; Approved November 9, 1999.

2. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
   [Vol. A1.1 pg. 82]

2. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 19-921

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382892	Sep 02, 2003			III	None
4551456	Nov 14, 2003	U-80	METHOD OF TREATING OCULAR BACTERIAL INFECTIONS	III	NONE

Exclusivity-Data – NDA 19-921

Code	Reference	Expiration	Labeling Impact
ODE	ORPHAN DRUG EXCLUSIVITY	May 22, 2003	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight containers at controlled room temperature.
- RLD: Stored at 15° to 25°C (59° to 77°F).
- ANDA: Store at 15° to 25°C (59° to 77°F).

5. DISPENSING STATEMENT COMPARISON

- USP: None.
- RLD: None.
- ANDA: None.

6. PACKAGE CONFIGURATION

- RLD: Packaged in 1 ml, 5 ml, and 10 ml plastic dropper bottles with a tan cap.
- ANDA: Packaged in 5 ml, and 10 ml plastic dropper bottles with a beige cap.

7. CONTAINER/CLOSURE

Packaged into White Round 10 cc Bottles with white, extended control dropper tip and (b) (4) cap.

Please note, the packaging component section does not include the 5ml packaging components.

8. FINISHED DOSAGE FORM

- RLD: Supplied as a 1 ml, 5 ml and 10 ml
- ANDA: A clear, (b) (4) solution supplied as 5 ml and 10 ml bottles.

[Vol.1.2, pages 610 and 612]

9. CAP COLOR

- RLD: Tan color cap
- ANDA Beige color cap (Vol. 1.2, page 571)

10. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Bausch & Lomb Pharmaceuticals, Inc.
Hidden River Maufacturing Facility
8500 Hidden River Parkway
Tampa, Florida 33637
[Vol. A1.1 pg. 186]

Date of Review: **Date of Submission: June 16, 2003**

Primary Reviewer: Beverly Weitzman **Date:** 8/04/2003

B. Weitzman

Team Leader: **Date:** 8/5/2003

cc:

ANDA: 76-622
DUP/DIVISION FILE
HFD-613/Jgrace (no cc)
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Review

APPROVAL SUMMARY

Supercedes June 16, 2003 submission

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-622

Date of Submission: March 16, 2004 and April 22, 2004 (Amendment for Container Label)

Applicant's Name: Bausch & Lomb

Established Name: Ofloxacin Ophthalmic Solution USP, 0.3%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? YES
Container Labels: (5 mL and 10 mL) – Satisfactory in Final Printed Label as of April 22, 2004.
Carton Labeling: (5 mL and 10 mL) – Satisfactory in Final Printed Label as of March 16, 2004.
Professional Package Insert Labeling: Satisfactory in final printed labeling as of March 16, 2004 submission. [Revised 2/04; Code # X051054 (folded); XM10124 (flat)]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Ocuflox Ophthalmic Solution, 0.3%
- NDA Number: 19-921/S008
- NDA Drug Name: Ofloxacin Ophthalmic Solution, 0.3%
- NDA Firm: Allergan Inc
- Date of Approval of NDA Insert: Approved November 9, 1999
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.
- Comment: 1) Please note on all labeling, the name of the manufacturer has been changed from Bausch and Lomb Pharmaceuticals to Bausch and Lomb Incorporated. The enclosed labeling has no other changes from that previously reviewed from the June 16, 2003 submission.

Patent Data – NDA 19-921

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382892	SEP 02, 2003			III	None
4382892*PED	MAR 02, 2004			III	NONE
4551456	NOV 14, 2003	U-80	METHOD OF TREATING OCULAR BACTERIAL INFECTIONS	III	NONE
4551456*PED	MAY 14, 2004	U-80		III	NONE

Exclusivity-Data – NDA 19-921

Code	Reference	Expiration	Labeling Impact
ODE	ORPHAN DRUG EXCLUSIVITY	MAY 22, 2003	NONE
PED		NOV 22, 2003	NONE

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

The firm did not include the 5 ml bottle size in the packaging component section, (Vol. 1.2 section XII, page 459). 10ml bottle is used for both 5ml and 10ml fill sizes. Ope Kanuy 5/3/04

FOR THE RECORD:

1. **MODEL LABELING**

This review was based on the labeling for Occuflox by Allergan Inc.; NDA 19-921/S008; Revised November 2000; Approved November 9, 1999.

2. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
[Vol. A1.1 pg. 82]

3. **PATENTS/EXCLUSIVITIES**

Patent Data – NDA 19-921

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382892	SEP 02, 2003			III	None
4382892*PED	MAR 02, 2004			III	NONE
4551456	NOV 14, 2003	U-80	METHOD OF TREATING OCULAR BACTERIAL INFECTIONS	III	NONE
4551456*PED	MAY 14, 2004	U-80		III	NONE

Exclusivity-Data – NDA 19-921

Code	Reference	Expiration	Labeling Impact
ODE	ORPHAN DRUG EXCLUSIVITY	MAY 22, 2003	NONE
PED		NOV 22, 2003	NONE

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
- USP: Preserve in tight containers at controlled room temperature.
- RLD: Stored at 15° to 25°C (59° to 77°F).
- ANDA: Store at 15° to 25°C (59° to 77°F).

5. **DISPENSING STATEMENT COMPARISON**
- USP: None.
- RLD: None.
- ANDA: None.

6. **PACKAGE CONFIGURATION**
- RLD: Packaged in 1 ml, 5 ml, and 10 ml plastic dropper bottles with a tan cap.
- ANDA: Packaged in 5 ml, and 10 ml plastic dropper bottles with a beige cap.

7. **CONTAINER/CLOSURE**
Packaged into White Round 10 cc Bottles with white, extended control dropper tip and (b) (4) cap.
Please note, the packaging component section does not include the 5ml packaging components.

8. **FINISHED DOSAGE FORM**
- RLD: Supplied as a 1 ml, 5 ml and 10 ml
- ANDA: A clear, (b) (4) solution supplied as 5 ml and 10 ml bottles.

[Vol.1.2, pages 610 and 612]

9. **CAP COLOR**
- RLD: Tan color cap
- ANDA Beige color cap (Vol. 1.2, page 571)

10. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
Bausch & Lomb Pharmaceuticals, Inc.
Hidden River Maufacturing Facility
8500 Hidden River Parkway
Tampa, Florida 33637
[Vol. A1.1 pg. 186]

Date of Review: **Date of Submission:** March 16, 2004 and April 22, 2004

Primary Reviewer: Beverly Weitzman S. Weitzman **Date:** 4/26/04

Team Leader: **Date:**

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cc:

ANDA: 76-622
DUP/DIVISION FILE
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Review

Page 4/28/04 for John Grace

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

CHEMISTRY REVIEWS

ANDA 76-622

Ofloxacin Ophthalmic Solution, 0.3%, USP

Bausch & Lomb

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-622

2. REVIEW #: 1

3. REVIEW DATE: 24-JUN-2003

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	31-DEC-2002
New correspondence	12-FEB-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Bausch & Lomb Pharmaceuticals, Inc.
Address:	8500 Hidden River Parkway Tampa, FL 33637
Representative:	Joseph B. Hawkins
Telephone:	(813) 866-2102

Fax (813) 975-7757

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Ofloxacin Ophthalmic Solution

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Ocuflox Allergan, Inc.
Application Number:	N019921
Strength:	0.3%
Patent Certification:	Paragraph III Certification (Bausch & Lomb certifies that U.S. patent No. 4,382,892 will expire on 02-SEP-2003 and that U.S. patent 4,511,456 will expire on 14-NOV-2003.)
Exclusivity:	Expired on 22-MAY-2003 (Exclusivity Code; ODE).

10. PHARMACOL. CATEGORY:
Bacterial conjunctivitis and corneal ulcers

11. DOSAGE FORM:
Ophthalmic Solution

12. STRENGTH/POTENCY:
0.3%

13. ROUTE OF ADMINISTRATION:
Ophthalmic

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

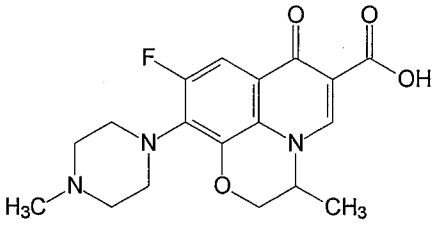
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piper-azinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

$C_{18}H_{20}FN_3O_4$ Mol. wt. 361.38
CAS number: 82419-36-1



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS 2	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	Adequate	3	07-DEC-2002	
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					7		Additional data are requested.
					7		Additional data are requested.
					4		<USP>661 test data are included.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A, Compendial		
Labeling	Not Acceptable	28-MAY-2003	B. Weitzman
Bioequivalence	Pending		
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-622

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval (minor amendment).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Ocuflox (Ofloxacin Ophthalmic Solution, 0.3%), by Allergan and approved on July 30, 1990. Ofloxacin Ophthalmic Solution, 0.3% is indicated for bacterial conjunctivitis and bacterial corneal ulcers.

The drug substance is Ofloxacin, USP and conforms to the USP monograph. The drug substance is a white to cream-white odorless powder and (b) (4) by the drug substance manufacturer. The applicant proposes the related substance specifications based on the actual test result and they are tighter than the drug substance manufacturer's specifications.

The drug product is also a USP article and contains as excipients; Benzalkonium chloride, sodium chloride and purified water, hydrochloric acid and/or sodium chloride to adjust pH.

The drug product is manufactured (b) (4)

Stability batches were packaged in 5 mL and 10 mL bottles and stored at accelerated (40 ± 2°C °C/20 ± 5%) and long-term conditions. Overall, the drug product release and stability data support the firm's proposed specifications.

B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
Not approvable

III. Administrative

A. Reviewer's Signature
G.Kang/HFD-627 GK 6/25/03

B. Endorsement Block

Chemist, G. Kang/HFD-627/
Chemistry Team Leader, J. Fan/HFD-627/
Project Manager, A.Vu/HFD-617/

D. CC Block

ANDA #76-622
ANDA #76-622/Division File
Field Copy

Following this page, 16 pages withheld in full (b)(4)-CCI/TS

(b) (4)

[redacted]

30. MICROBIOLOGY

Review status: Pending

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Review status: N/A

Both the drug substance and product are listed in the USP. FDA method validation is not required.

32. LABELING

Review status: Not acceptable

Reviewed by B. Weitzman and found deficient on 28-MAY-2003.

33. ESTABLISHMENT INSPECTION

Review status: Pending

34. BIOEQUIVALENCE

Review status: Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review status: Satisfactory

A waiver was submitted on page 1041.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-622 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Ofloxacin Ophthalmic Solution USP, 0.3%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence and microbiology sections of your application are under review and you will be notified separately of any deficiencies.

2. A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval.

3. Please provide all available updated drug product long-term room temperature stability data for our evaluation.

Sincerely yours,

Paul Shrivastava 6/26/03

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-622
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/6/25/03 GK 6/25/03

HFD-627/J. Fan, Team Leader/6/25/03 6/26/03

HFD-617/ A. Vu, PM/6/25/03

F/T by:ard/6/25/03

V:\FIRMSAM\BAUSCH\LTRS&REV\76622NA1.1RD.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-622

Ofloxacin Ophthalmic Solution, 0.3%, USP

Bausch & Lomb

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-622

2. REVIEW #: 2

3. REVIEW DATE: 02-OCT-2003

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original	31-DEC-2002
New correspondence	12-FEB-2003
Deficiency letter based on review #1	26-JUN-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment	07-JUL-2003
Telephone amendment	02-OCT-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Bausch & Lomb Pharmaceuticals, Inc.
Address:	8500 Hidden River Parkway Tampa, FL 33637
Representative:	Joseph B. Hawkins

Telephone: (813) 866-2102

Fax (813) 975-7757

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Ofloxacin Ophthalmic Solution

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Ocuflox Allergan, Inc.
Application Number:	N019921
Strength:	0.3%
Patent Certification:	Paragraph III Certification (Bausch & Lomb certifies that U.S. patent No. 4,382,892 will expire on 02-SEP-2003 and that U.S. patent 4,511,456 will expire on 14-NOV-2003.)
Exclusivity:	Expired on 22-MAY-2003 (Exclusivity Code; ODE).

10. PHARMACOL. CATEGORY:
Bacterial conjunctivitis and corneal ulcers

11. DOSAGE FORM:
Ophthalmic Solution

12. STRENGTH/POTENCY:
0.3%

13. ROUTE OF ADMINISTRATION:
Ophthalmic

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

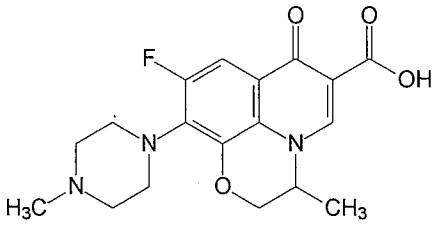
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piper-azinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

$C_{18}H_{20}FN_3O_4$ Mol. wt. 361.38
CAS number: 82419-36-1



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS 2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				Adequate	3	07-DEC-2002	
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	**Not acceptable**	17-OCT-2003	
EES	Acceptable	30-JUN-2003	
Methods Validation	N/A		
Labeling	Acceptable	05-AUG-2003	B. Weitzman
Bioequivalence	The wavier is granted.	05-SEP-2003	J. L. Osterhout
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor

The Chemistry Review for ANDA 76-622

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The review of microbiology section is deficient.
Chemistry, bioequivalency and labeling sections are recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Ocuflox (Ofloxacin Ophthalmic Solution, 0.3%), by Allergan and approved on July 30, 1990. Ofloxacin Ophthalmic Solution, 0.3% is indicated for bacterial conjunctivitis and bacterial corneal ulcers.

The drug substance is Ofloxacin, USP and conforms to the USP monograph. The drug substance is a white to cream-white odorless powder and (b) (4) by the drug substance manufacturer. The applicant proposes the related substance specifications based on the actual test result and they are tighter than the drug substance manufacturer's specifications.

The drug product is also a USP article and contains as excipients; .Benzalkonium chloride, sodium chloride and purified water, hydrochloric acid and/or sodium chloride to adjust pH.

The drug product is manufactured (b) (4)

Stability batches were packaged in 5 mL and 10 mL bottles and stored at accelerated (40 ± 2°C °C/20 ± 5%) and long-term conditions. Overall, the drug product release and stability data support the firm's proposed specifications.

B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
In response to the Agency request, the firm has revised the "description test" and "weight/gain test" specifications to reflect the acceptance criteria stated on the Marketed Stability Protocol.
Chemistry section is approvable.

III. Administrative

A. Reviewer's Signature
G.Kang/HFD-627

B. Endorsement Block

Chemist, G. Kang/HFD-627/
Chemistry Team Leader, J. Fan/HFD-627/
Project Manager, A.Vu/HFD-617/

D. CC Block

ANDA #76-622
ANDA #76-622/Division File
Field Copy

Following this page, 11 pages withheld in full (b)(4)-CCI/TS

(b) (4)

30. MICROBIOLOGY

Review status: Not Acceptable on 17-OCT-2003 by N. Nath

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Review status: N/A

FDA method validation is not required per OGD policy.

32. LABELING

Review status: acceptable on 05-AUG-2003

28-MAY-2003	Reviewed by B. Weitzman and found deficient.
16-JUN-2003	Amendment
05-AUG-2003	Reviewed by B. Weitzman and found acceptable.

33. ESTABLISHMENT INSPECTION

Review status: acceptable on 30-JUN-2003

34. BIOEQUIVALENCE

Review status: acceptable on 05-SEP-2003

A request of in-vivo bioavailability waiver has been reviewed by J. Osterhout and granted on 05-SEP-2003.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review status: Satisfactory

A waiver was submitted on page 1041.

36 . CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-622 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Ofloxacin Ophthalmic Solution USP, 0.3%

The deficiency presented below represents a MINOR deficiency:

A. Deficiency:

Microbiology deficiencies were communicated to you via facsimile on October 22, 2003. You should address the issues in the October 22, 2003 communication prior to or concurrent with your response to this communication.

Sincerely yours,

11/4/03

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-622
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/9/29/03 GK 10/30/03

HFD-627/J. Fan, Team Leader/ 11/3/03

HFD-617/ A. Vu, PM/

F/T by:ard/10/30/03

V:\FIRMSAM\BAUSCH\LTRS&REV\76622NA1.2RD.doc

NOT APPROVABLE

ANDA 76-622

Ofloxacin Ophthalmic Solution USP, 0.3%

Bausch & Lomb

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-622

2. REVIEW #: 3

3. REVIEW DATE: 18-DEC-2003

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original	31-DEC-2002
New correspondence	12-FEB-2003
Deficiency letter based on review #1	26-JUN-2003
Minor amendment	07-JUL-2003
Telephone amendment	02-OCT-2003
Deficiency letter based on review #2	05-NOV-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment (Microbiology)	11-NOV-2003
Telephone amendment (Patent certification)	07-JAN-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch & Lomb Pharmaceuticals, Inc.

Address: 8500 Hidden River Parkway
Tampa, FL 33637

Representative: Joseph B. Hawkins

Telephone: (813) 866-2102

Fax (813) 975-7757

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Ofloxacin Ophthalmic Solution

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Ocuflox Allergan, Inc.
Application Number:	N019921
Strength:	0.3%
Patent Certification:	Paragraph II Certification (Bausch & Lomb certifies that U.S. patent No. 4,382,892 expires on 02-SEP-2003 and that U.S. patent 4,511,456 expires on 14-NOV-2003.)
Exclusivity:	Expired on 22-MAY-2003 (Exclusivity Code; ODE). Pediatric exclusivity expires on 14-MAY-2004 for patent '456.

10. PHARMACOL. CATEGORY:
Bacterial conjunctivitis and corneal ulcers

11. DOSAGE FORM:
Ophthalmic Solution

12. STRENGTH/POTENCY:
0.3%

13. ROUTE OF ADMINISTRATION:
Ophthalmic

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

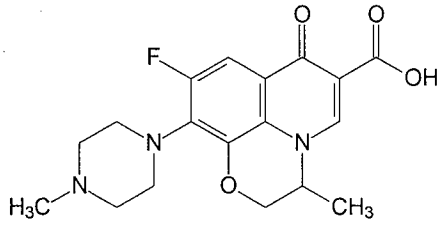
_____SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piper-azinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

$C_{18}H_{20}FN_3O_4$ Mol. wt. 361.38
CAS number: 82419-36-1



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				Adequate	3	29-DEC-2003	By R. Murali
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	01-DEC-2003	N.Nath
EES	Acceptable	30-JUN-2003	
Methods Validation	N/A		
Labeling	Acceptable	05-AUG-2003	B. Weitzman
Bioequivalence	The wavier is granted.	05-SEP-2003	J. L. Osterhout
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor

The Chemistry Review for ANDA 76-622

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Microbiology section became acceptable on 01-DEC-2003.
Overall, the application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Ocuflox (Ofloxacin Ophthalmic Solution, 0.3%), by Allergan and approved on July 30, 1990. Ofloxacin Ophthalmic Solution, 0.3% is indicated for bacterial conjunctivitis and bacterial corneal ulcers.

The drug substance is Ofloxacin, USP and conforms to the USP monograph. The drug substance is a white to cream-white odorless powder and (b) (4) by the drug substance manufacturer. The applicant proposes the related substance specifications based on the actual test result and they are tighter than the drug substance manufacturer's specifications.

The drug product is also a USP article and contains as excipients; Benzalkonium chloride, sodium chloride and purified water, hydrochloric acid and/or sodium chloride to adjust pH.

The drug product is manufactured (b) (4)

Stability batches were packaged in 5 mL and 10 mL bottles and stored at accelerated (40 ± 2°C °C/20 ± 5%) and long-term conditions. Overall, the drug product release and stability data support the firm's proposed specifications.

B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
Microbiology section became acceptable on 01-DEC-2003.
The application is now approvable.

III. Administrative

A. Reviewer's Signature
G.Kang/HFD-627

B. Endorsement Block

GK 1/20/04
Chemist, G. Kang/HFD-627/12/18/03
Chemistry Team Leader, J. Fan/HFD-627/12/24/03
Project Manager, A.Vu/HFD-617/

D. CC Block

ANDA #76-622
ANDA #76-622/Division File
Field Copy

Following this page, 9 pages withheld in full (b)(4)-CCI/TS

(b) (4)

30. MICROBIOLOGY

Review status: Acceptable on 12/1/03 by N. Nath

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Review status: N/A

FDA method validation is not required per OGD policy.

32. LABELING

Review status: acceptable on 05-AUG-2003

28-MAY-2003	Reviewed by B. Weitzman and found deficient.
16-JUN-2003	Amendment
05-AUG-2003	Reviewed by B. Weitzman and found acceptable.

33. ESTABLISHMENT INSPECTION

Review status: acceptable on 30-JUN-2003

34. BIOEQUIVALENCE

Review status: acceptable on 05-SEP-2003

A request of in-vivo bioavailability waiver has been reviewed by J. Osterhout and granted on 05-SEP-2003.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review status: Satisfactory

A waiver was submitted on page 1041.

cc: ANDA 76-622
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/12/18/03 GK 1/20/04

HFD-627/J. Fan, Team Leader/12/24/03 1/20/04

HFD-617/ A. Vu, PM/1/15/04 1/20/04

F/T by:ard/1/16/04

V:\FIRMSAM\BAUSCH\LTRS&REV\76622NA1.3RD.doc

APPROVABLE

ANDA 76-622

Ofloxacin Ophthalmic Solution USP, 0.3%

Bausch & Lomb

Gil-Jong Kang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-622

2. REVIEW #: 4

3. REVIEW DATE: 26-APR-2004

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original	31-DEC-2002
New correspondence	12-FEB-2003
Deficiency letter based on review #1	26-JUN-2003
Minor amendment	07-JUL-2003
Telephone amendment	02-OCT-2003
Deficiency letter based on review #2	05-NOV-2003
Minor amendment (Microbiology)	11-NOV-2003
Telephone amendment (Patent certification)	07-JAN-2004
Tentative approval	23-JAN-2004
Amendment (Labeling)	16-MAR-2004
Amendment (Labeling)	22-APR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment (for final approval)	12-MAR-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch & Lomb Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Address:	8500 Hidden River Parkway Tampa, FL 33637
Representative:	Joseph B. Hawkins
Telephone:	(813) 866-2102
Fax	(813) 975-7757

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Ofloxacin Ophthalmic Solution

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Ocuflox Allergan, Inc.
Application Number:	N019921
Strength:	0.3%
Patent Certification:	Paragraph II Certification (Bausch & Lomb certifies that U.S. patent No. 4,382,892 expires on 02-SEP-2003 and that U.S. patent 4,511,456 expires on 14-NOV-2003.)
Exclusivity:	Expired on 22-MAY-2003 (Exclusivity Code; ODE). Pediatric exclusivity expires on 14-MAY-2004 for patent '456.

10. PHARMACOL. CATEGORY:
Bacterial conjunctivitis and corneal ulcers

11. DOSAGE FORM:
Ophthalmic Solution

12. STRENGTH/POTENCY:
0.3%

13. ROUTE OF ADMINISTRATION:
Ophthalmic

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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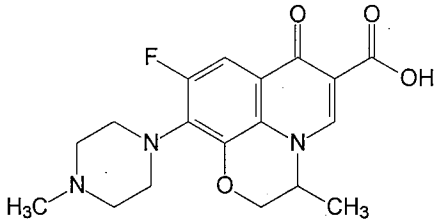
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piper-azinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

$C_{18}H_{20}FN_3O_4$ Mol. wt. 361.38
CAS number: 82419-36-1



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS 2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				Adequate	3	29-DEC-2003	By R. Murali
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.
					4		<USP>661 test data are included.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	01-DEC-2003	N.Nath
EES	Acceptable	30-JUN-2003	
Methods Validation	N/A		
Labeling	Acceptable	28-APR-2004	B. Weitzman
Bioequivalence	The wavier is granted.	05-SEP-2003	J. L. Osterhout
EA	Waiver		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor

The Chemistry Review for ANDA 76-622

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for final approval upon expiry of market exclusivity for the RLD on 14-MAY-2004.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Ocuflox (Ofloxacin Ophthalmic Solution, 0.3%), by Allergan and approved on July 30, 1990. Ofloxacin Ophthalmic Solution, 0.3% is indicated for bacterial conjunctivitis and bacterial corneal ulcers.

The drug substance is Ofloxacin, USP and conforms to the USP monograph. The drug substance is a white to cream-white odorless powder and (b) (4) by the drug substance manufacturer. The applicant proposes the related substance specifications based on the actual test result and they are tighter than the drug substance manufacturer's specifications.

The drug product is also a USP article and contains as excipients; Benzalkonium chloride, sodium chloride and purified water, hydrochloric acid and/or sodium chloride to adjust pH.

The drug product is manufactured (b) (4)

Stability batches were packaged in 5 mL and 10 mL bottles and stored at accelerated (40 ± 2°C °C/20 ± 5%) and long-term conditions. Overall, the drug product release and stability data support the firm's proposed specifications.

B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
The application is approvable.

III. Administrative

A. Reviewer's Signature
G.Kang/HFD-627

B. Endorsement Block

Chemist, G. Kang/HFD-627/ GK 5/4/04
Chemistry Team Leader, J. Fan/HFD-627/ 5/4/04
Project Manager, A.Vu/HFD-617/

D. CC Block

ANDA #76-622
ANDA #76-622/Division File
Field Copy

Following this page, 8 pages withheld in full (b)(4)-CCI/TS

(b) (4)

[redacted]

30. MICROBIOLOGY

Review status: Acceptable on 12/1/03 by N. Nath.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Review status: N/A

FDA method validation is not required.

32. LABELING

Review status: acceptable on 28-APR-2004

28-MAY-2003	Reviewed by B. Weitzman and found deficient.
16-JUN-2003	Amendment
28-APR-2004	Reviewed by B. Weitzman and found acceptable.

33. ESTABLISHMENT INSPECTION

Review status: acceptable on 30-JUN-2003

34. BIOEQUIVALENCE

Review status: acceptable on 05-SEP-2003

A request of in-vivo bioavailability waiver has been reviewed by J. Osterhout and granted on 05-SEP-2003.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review status: Satisfactory

A waiver was submitted on page 1041.

cc: ANDA 76-622
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /G. Kang/ GK 5/4/04

HFD-627/J. Fan, Team Leader/ 5/4/04

HFD-617/ A. Vu, PM/

F/T by:

V:\FIRMSAM\BAUSCH\LTRS&REV\76622NA1.4RD.doc

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-622
Drug Product Name	Ofloxacin Ophthalmic Solution
Strength	0.3%
Applicant Name	Bausch & Lomb Pharmaceuticals
Address	8500 Hidden River Parkway, Tampa, Fl 33637
Submission Date(s)	January 02, 2003
Amendment Date(s)	N.A.
Reviewer	James L. Osterhout
First Generic	No
File Location	v:\firmsam\bausch\ltrs&rev\76622W0103.doc

I. Executive Summary

The firm has requested a waiver of in-vivo bioavailability requirements for Ofloxacin Ophthalmic Solution, 0.3% (sterile), 5 mL and 10 mL bottles. The reference-listed drug (RLD) is Allergan, Inc. Ocuflox® Ophthalmic Solution, 0.3% (sterile), available in 1 mL, 5 mL and 10 mL bottles. The firm has submitted comparative formulations of its Ofloxacin Ophthalmic Solution, 0.3% and Allergan, Inc. Ocuflox® Ophthalmic Solution, 0.3% in support of the biowaiver request. The test and RLD products have the same formulation. The biowaiver request is granted based on 21CFR320.22(b)(1).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Ofloxacin Ophthalmic Solution, 0.3% (sterile) 5 mL and 10 mL bottle
Reference Product	Ocuflox® Ophthalmic Solution, 0.3% (sterile) 1 mL, 5 mL and 10 mL bottle
RLD Manufacturer	Allergan, Inc
NDA No.	19-921
RLD Approval Date	30 July 1993
Indication	Ofloxacin is indicated for the treatment of corneal ulcers caused by bacteria and for bacterial conjunctivitis.

B. PK/PD Information

Bioavailability	97.6% (tablet, 3x100mg)
Food Effect	Food increases the Tmax of ofloxacin
Tmax	1.60 hours single dose (day 1, ophthalmic) 1.06 hours multiple dose (day 11, ophthalmic)
Metabolism	N.A.
Excretion	Ofloxacin is excreted in the urine primarily unmodified.
Half-life	3.0-5.3 hours (PO dose, NDA#19-735)
Relevant OGD or DBE History	There are numerous ANDA's for the tablet form of Ofloxacin. ANDA# 75-762: Waiver granted for Ofloxacin Injection, 40 mg/mL vial. ANDA# 76-128: Waiver granted for Ofloxacin Otic Solution, 0.3%. ANDA# 76-231: Waiver granted to Alcon Research, Inc. for Ofloxacin Ophthalmic Solution, 0.3% ANDA# 76-407: Waiver granted to Akorn, Inc. for Ofloxacin Ophthalmic Solution, 0.3%. ANDA# 76-513: Waiver granted to Novex Pharma for Ofloxacin Ophthalmic Solution, 0.3%. ANDA# 76-527: Waiver granted to Novex Pharma for Ofloxacin Otic Solution, 0.3%. ANDA# 76-616: In process, Ofloxacin Otic Solution, 0.3%.
Agency Guidance	Waiver of BE study requirements granted based on the same active and inactive ingredients as the RLD
Drug Specific Issues	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	2
BCS Waivers	No	--
Vasoconstrictor Studies	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

D. Formulation

Location in appendix	Section H, Page 5
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	--
If a tablet, is the product scored? (yes or no)	--
If yes, which strengths are scored?	--
Is scoring of RLD the same as test? (yes or no)	--
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	--

E. Waiver Request(s)

Strengths for which waivers requested	0.3%
Regulation cited	21CFR320.22(b)(1)
Proportional to strength tested in vivo (yes or no)	N.A.
Dissolution is acceptable (yes or no)	N.A.
Waiver granted (yes or no)	Yes

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22(b)(1) for the following strength(s): 0.3%, 5 mL and 10 mL bottle.

F. Deficiency Comments

None

G. Recommendations

The Division of Bioequivalence agrees that the information submitted by Bausch & Lomb Pharmaceuticals demonstrates that its Ofloxacin Ophthalmic Solution, 0.3%, 5 mL and 10 mL bottle fall under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

Therefore, the Division of Bioequivalence recommends that a waiver of in-vivo bioequivalence study requirements for Ofloxacin Ophthalmic Solution, 0.3%, 5 mL and 10 mL bottle be granted. The test product is deemed bioequivalent to Allergan, Inc. Ocuflox® 0.3%, 5 mL and 10 mL bottle.

James Osterhout, Reviewer, Branch I — Date 9/4/03

Yih Chain Huang, Ph.D., Team Leader, Branch I — Date 9/4/2003

for Barbara M. Davit — 9/5/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

H. Formulation Data

	Bausch & Lomb Pharmaceuticals Ofloxacin Ophthalmic Solution, 0.3%	Allergan Ocuflox® Ofloxacin Ophthalmic Solution, 0.3% NDA# 19-921
Ingredients	**mg/mL**	
Ofloxacin, USP	3.0	3.0
Benzalkonium Chloride, USP	(b) (4)	(b) (4)
Sodium Chloride, USP		
Sodium Hydroxide, NF	pH adjust	pH adjust
Hydrochloric Acid, NF	pH adjust	pH adjust
Water (b) (4)	qs to volume	qs to volume

The formulation for the RLD is from COMIS.

The RLD (and test) solution is targeted to pH 6.4±0.4.

I. Consult Reviews

None

J. Additional Attachments

None

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-622 APPLICANT: Bausch & Lomb Pharmaceuticals

DRUG PRODUCT: Ofloxacin Ophthalmic Solution, 0.3%, 5 mL and 10 mL bottles

The Division of Bioequivalence has completed its review and has no further questions at this time.

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,

for Barbara Myers Davit

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-622
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer J.L. Osterhout
HFD-617/ Project manager A.W. Sigler
HFD-652/ Team Leader Y.C. Huang

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Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout 9/4/03
HFD-652/ Y.C. Huang 9/4/2003
for HFD-650/ D.P. Conner 9/5/03

BIOEQUIVALENCY - ACCEPTABLE Submission date: January 2, 2003

1. WAIVER (WAI) OIC Strengths: 0.3% (5 mL and 10 mL bottles)

Outcome: AC

Outcome Decisions: AC – Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-622 **SPONSOR:** Bausch & Lomb Pharmaceuticals

DRUG AND DOSAGE FORM: Ofloxacin Ophthalmic Solution

STRENGTH(S): 0.3%, 5 mL and 10 mL bottles

TYPES OF STUDIES: N/A

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

STUDY SUMMARY: The waiver is granted

DISSOLUTION: N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic NO New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : James L. Osterhout, Ph.D. **BRANCH :** I

INITIAL : JLO **DATE :** 9/4/03

TEAM LEADER : Yih-Chain Huang, Ph.D. **BRANCH :** I

INITIAL : YCH **DATE :** 9/4/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm.D.

INITIAL : DPC **DATE :** 9/5/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-620

11 August 2003

ANDA: 76-622

Drug Product Name
Proprietary: N/A
Non-proprietary: Ofloxacin Ophthalmic Solution, 0.3%
Drug Product Classification: Anti-infective

Review Number: #1

Subject of this Review
Submission Date: December 31, 2002
Receipt Date: January 2, 2003
Consult Date: N/A
Date Assigned for Review: August 1, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Bausch and Lomb Pharmaceuticals
Address: 8500 Hidden Valley Parkway, Tempa, FL 33637
Representative: Joseph B. Hawkins
U.S. Agent: N/A
Telephone: 813-866-2102

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Bausch and Lomb Pharmaceuticals
8500 Hidden Valley Parkway
Tempa, FL 33637

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 5 mL in 10mL and 10mL in 10-mL bottle; ophthalmic 0.3% solution.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Anti-infective

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:** The subject ANDA 76-622 is similar to the ANDA 76-128 for Ofloxacin Otic Solution, 0.3% (Sterile), which was reviewed by the subject reviewer in September 2001.

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The subject drug product is [redacted] (b) (4) on [redacted] (b) (4) lines #1, 9 and 10 as 5mL and 10mL dose form in 10-mL plastic bottles, fitted with a 15mm Tip and closed with a cap.

B. Brief Description of Microbiology Deficiencies -

Insufficient data and details are provided to support validation of sterilization [redacted] (b) (4).

C. Assessment of Risk Due to Microbiology Deficiencies -

Low.

III. Administrative

A. Reviewer's Signature Nrapendra Nath 10/17/03

B. Endorsement Block Neal J Sweeney 10-17-03

Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney

C. CC Block

cc:
Original ANDA
HFD- 600/Division File
Field Copy

filename: V:\Microrev\ 76-622.doc

Following this page, 16 pages withheld in full (b)(4)-CCI/TS

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 76-622 APPLICANT: Bausch & Lomb

DRUG PRODUCT: Ofloxacin Ophthalmic Solution 0.3%

A. Microbiology Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.

8. (b) (4)

9.

10.

Please clearly identify your amendment to this facsimile as RESPONSE TO MICROBIOLOGY DEFICIENCIES. The RESPONSE TO MICROBIOLOGY DEFICIENCIES should also be noted in your cover page/letter.

Sincerely yours,

Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

Product Quality Microbiology Review
Review for HFD-620

25 November 2003

ANDA: 76-622

Drug Product Name
Proprietary: N/A
Non-proprietary: Ofloxacin Ophthalmic Solution, 0.3%
Drug Product Classification: Anti-infective

Review Number: #2

Subject of this Review
Submission Date: November 11, 2003
Receipt Date: November 13, 2003
Consult Date: N/A
Date Assigned for Review: November 24, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): December 31 (original)
Date(s) of Previous Micro Review(s): August 11, 2003

Applicant/Sponsor
Name: Bausch and Lomb Pharmaceuticals
Address: 8500 Hidden Valley Parkway, Tempa, FL 33637
Representative: Joseph B. Hawkins
U.S. Agent: N/A
Telephone: 813-866-2102

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Bausch and Lomb Pharmaceuticals
8500 Hidden Valley Parkway
Tempa, FL 33637

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 5 mL in 10mL and 10mL in 10-mL bottle; ophthalmic 0.3% solution.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Anti-infective

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:** None.

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" section.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The subject drug product is [redacted] (b) (4) on [redacted] (b) (4) lines #1, 9 and 10 as 5mL and 10mL dose form in 10-mL plastic bottles, fitted with a 15mm Tip and closed with a cap.

B. Brief Description of Microbiology Deficiencies -
None.

C. Assessment of Risk Due to Microbiology Deficiencies -
N/A.

III. Administrative

A. Reviewer's Signature Nrapendra Nath 12/1/03

B. Endorsement Block
Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney Neal J Sweeney 12-1-03

C. CC Block
cc:
Original ANDA
HFD- 600/Division File
Field Copy

Filename: V:\Microrev\ 76-622a1.doc

Following this page, 5 pages withheld in full (b)(4)- CCI/TS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076622

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

8500 Hidden River Parkway
Tampa FL 33637

www.bausch.com

BAUSCH
& LOMB

December 31, 2002

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

505(b)(2) NDA
13-FEB-2003

Re: Ofloxacin Ophthalmic Solution, 0.3% (Sterile) ANDA Submission

Dear Sir or Madam:

In accordance with the provisions set forth in 21 CFR 314.94, we are submitting this abbreviated new drug application, in duplicate, for Ofloxacin Ophthalmic Solution, 0.3% (Sterile).

This application is composed of five original volumes, including sterility assurance data in Section XXII. An additional volume (Sterility Assurance Desk Copy of Chemistry Sections) contains copies of this cover letter, labeling and package insert comparison, components and composition statements, and the exhibit batch record. This volume contains no original information. An analytical methods validation package, which includes two additional copies of non-compendial assay procedures and the corresponding validation studies, is provided under separate cover. We will commit to resolve any issues identified in the methods validation process after approval.

Changes which influence the manufacture of Ofloxacin Ophthalmic Solution, 0.3% (Sterile), will be reported to the Agency as established in 21 CFR 314.70.

In accordance with 21 CFR 314.94 (d)(5), we certify that a true copy of the information contained in this application has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 866-2102 or facsimile (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Manager
Regulatory Affairs

Enclosures

RECEIVED
JAN 02 2003
OGD / CDER

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

February 12, 2003

NEW CORRESP
NC

76-622

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: Ofloxacin Ophthalmic Solution, 0.3%, USP (Sterile)
Original Application
Response to Telephone Request

Dear Sir or Madam:

The purpose of this submission is to respond to a February 11, 2003 telephone request relayed by Emily Thomas, from the Office of Generic Drugs. A Table of Contents listing the requested items is provided immediately following the FDA Form 356H.

As required by 21 CFR 314.96(b), we certify that a field copy, which contains a true copy of the technical sections of this response, has been submitted to FDA's Maitland District Office.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this response, please do not hesitate to contact the undersigned by phone at (813) 866-2102, or by facsimile at (813) 975-7757.

Sincerely,

JB Hawk

Joseph B. Hawkins
Manager, Regulatory Affairs

Enclosure

ANDA 76-622

FEB 20

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated February 11, 2003 and your correspondence dated February 12, 2003.

NAME OF DRUG: Ofloxacin Ophthalmic Solution USP, 0.03%

DATE OF APPLICATION: December 31, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 2, 2003

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sarah Ho
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-622
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB GDavis 13-FEB-2003 date
HFD-615/EThomas, CSO 2/13/03 date
Word File V:\Firmsam\bausch\ltrs&rev\76622.ack
F/T EST02/13/03
ANDA Acknowledgment Letter!

8500 Hidden River Parkway
Tampa FL 33637

www.bausch.com

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& LOMB

June 16, 2003

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, Maryland 20855-2733

ORIG AMENDMENT
N/AFI

RE: ANDA 76-622, Ofloxacin Ophthalmic Solution USP, 0.3%
Labeling Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address comments received in a fax letter on June 5, 2003 regarding the above-referenced application. A copy of the Agency's fax is enclosed in Attachment 1.

Our response to the Agency's comments is provided following the form 356h. A side-by-side comparison and twelve copies of the revised package insert are enclosed.

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.

If you have any questions regarding this correspondence or need additional information, please contact me by telephone at (813) 866-2121 or by fax at (813) 975-7757.

Sincerely,

Gladys P. Martin
Director, Regulatory Affairs

Enclosure

RECEIVED
JUN 19 2003
OGD / CDER

MINOR AMENDMENT

ANDA 76-622

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)

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc. TEL: 813-866-2102

ATTN: Joseph B. Hawkins FAX: 813-975-7757

FROM: Thuyanh Vu PROJECT MANAGER: 301-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ofloxacin Opthalmic Solution USP, 0.3%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (two pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of 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. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC comments enclosed.

6/26/03

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-622 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Ofloxacin Ophthalmic Solution USP, 0.3%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

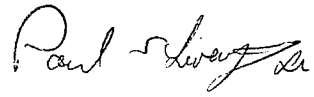
B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence and microbiology sections of your application are under review and you will be notified separately of any deficiencies.

2. A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval.

3. Please provide all available updated drug product long-term room temperature stability data for our evaluation.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

8500 Hidden River Parkway
Tampa FL 33637

www.bausch.com

July 7, 2003

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

ORIG AMENDMENT
N/AM

RE: ANDA 76-622
Ofloxacin Ophthalmic Solution USP, 0.3%
Minor Amendment
Response to Chemistry Deficiencies

Dear Sir or Madam:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the Agency's correspondence provided via facsimile on June 26, 2003. In that letter, the Agency indicated that our response would be considered a Minor Amendment. A copy of the Agency's June 26, 2003 correspondence is provided in Attachment 1.

To facilitate your review, each of the Agency's observations and our corresponding response is enclosed with this letter. A Table of Contents for the enclosed information is provided immediately following the Form FDA 356h.

As required by 21 CFR 314.96(b), we certify that a field copy, which contains a true copy of the technical sections of this amendment, has been submitted to FDA's Maitland District Office.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact me by telephone at (813) 866-2102 or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Director, Regulatory Affairs
Enclosures

RECEIVED
JUL 09 2003
OGD/CDER

MW 7/14/03

RECORD OF TELEPHONE CONVERSATION

Agency initiated firm to clarify July 7, 2003 minor amendment. Specificly, the stability protocol was inconsitent.

Agency: On page 39 and 40 (Attach 8) of your 7/7/03 minor amendment, the test name, test specification, test method was not consistent with your marketed stability protocol summary submitted in our original submission. Perhaps you mistakenly added the figures from your pre-marketed stability protocol instead of using the figures from your marketed stability protocol. For example, your test method for description shuld be P-1008, but your minor amendment stated P-1008 and 23-T132. You need to be consistent.

Firm: Understood. How do we submit this?

Agency: If it's easily solved, then submit as a t-amendment. You have 10 days. After 10 days, we will send out a chem def.

Firm: Understood, we will try to submit a t-amendment.

DATE:
9/30/03

ANDA NUMBER
76-622

TELECON INITIATED BY
Agency

PRODUCT NAME
Ofloxacin Opthalmic Solution, 0.3%

FIRM NAME:

Bausch & Lomb

FIRM REPRESENTATIVES:

(b) (6)

TELEPHONE NUMBER:
813-866-2121

FDA REPRESENTATIVES
Ann Vu

SIGNATURES:

Orig: 76-622
Cc: Division File
V:\FIRMSAM\BAUSCH\TELECONS\76622.30sep03.doc

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

October 2, 2003

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

ORIG AMENDMENT
N/am

RE: ANDA 76-622
Ofloxacin Ophthalmic Solution USP, 0.3%
Telephone Amendment

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's telephone request made during the telephone conversation on September 30, 2003 between (b) (6) and (b) (6) of Bausch & Lomb and Ann Vu with the FDA. The request was for clarification to our July 7, 2003 chemistry submission. A description of our response is provided immediately following the Form FDA 356h.

As required by 21 CFR 314.96(b), we certify that a field copy, which contains a true copy of the technical sections of this amendment, has been submitted to FDA's Maitland District Office.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact me by telephone at (813) 866-2102 or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Director, Regulatory Affairs
Enclosures

RECEIVED
OCT 0 6 2003
OGD/CDER

NW 10/6/03

ANDA 76-622

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc. TEL: 813-866-2102

ATTN: Joseph B. Hawkins FAX: 813-975-7757

FROM: Thuyanh Vu PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ofloxacin Ophtalmic Solution USP, 0.3%.

SPECIAL INSTRUCTIONS:
Microbiology comments provided.

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 76-622 APPLICANT: Bausch & Lomb

DRUG PRODUCT: Ofloxacin Ophthalmic Solution 0.3%

A. Microbiology Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.

(b) (4)

8.

9.

10.

Please clearly identify your amendment to this facsimile as RESPONSE TO MICROBIOLOGY DEFICIENCIES. The RESPONSE TO MICROBIOLOGY DEFICIENCIES should also be noted in your cover page/letter.

Sincerely yours,

Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 76-622

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)

NOV - 5 2003

APPLICANT: Bausch and Lomb

TEL: 813-866-2102

ATTN: Joseph Hawkins

FAX: 813-975-7757

FROM: Thuyan Vu

PROJECT MANAGER: 301-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ofloxacin Ophthalmic Solution USP, 0.3%.

Reference is also made to your amendment(s) dated: July 7 and October 2, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of 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. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC comments enclosed.

11/5/03

NOV – 5 2003

36 . CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-622 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Ofloxacin Ophthalmic Solution USP, 0.3%

The deficiency presented below represents a MINOR deficiency:

A. Deficiency:

Microbiology deficiencies were communicated to you via facsimile on October 22, 2003. You should address the issues in the October 22, 2003 communication prior to or concurrent with your response to this communication.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

November 11, 2003

BAUSCH & LOMB

ORIG AMENDMENT

N|RAM

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: ANDA 76-622, Ofloxacin Ophthalmic Solution, 0.3% (Sterile)
Minor Amendment - Response to Chemistry Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to address comments received in a fax on November 05, 2003 regarding the above referenced ANDA. A copy of the Agency's fax is enclosed. We have addressed the microbiology deficiencies communicated to us in the October 22, 2003 Agency letter.

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 supplement 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 or need additional information, please contact me by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Director,
Regulatory Affairs

enclosure

RECEIVED
NOV 13 2003
OGD/CDER

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

November 11, 2003

BAUSCH & LOMB

ORIG AMENDMENT

N|AS

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: ANDA 76-622, Ofloxacin Ophthalmic Solution, 0.3% (Sterile)
Minor Amendment - Response to Microbiology Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to address comments received in a fax on October 22, 2003 regarding the above referenced ANDA. A copy of the agency's fax is enclosed in Attachment 1.

This submission contains a complete response for each Agency comment, along with appropriate supporting documentation following the FDA form 356H.

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 supplement 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 or need additional information, please contact me by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Director,
Regulatory Affairs

enclosure

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NOV 13 2003
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Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

NAI Cullum 1/15/04

December 31, 2003

XP

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: Ofloxacin Ophthalmic Solution, 0.3% (Sterile) Telephone Amendment – Patent Certification

Dear Sir or Madam:

This correspondence is submitted in response to a December 30, 2003 telephone request from the Agency to provide an updated patent certification for the above reference ANDA.

Specifically, The Agency requested that we provide a Paragraph II patent certification for patents 4,382,892 and 4,551,456, and to acknowledge periods of exclusivity granted to the reference drug product. The requested certification is enclosed.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 866-2102 or facsimile (813) 975-7757.

Sincerely,

JB Hawk

Joseph B. Hawkins
Director,
Regulatory Affairs

Enclosure

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-622 Applicant Bausch + Lomb
Drug Ofloxacin Ophthalmic Solution Strength(s) 0.3%

PROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 12/30/03 Date 1/22/04 Rewritten
Initials MMS Initials

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = NDA#
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☑ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☑ Study Submitted ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Type of Letter:
Comments: from Has address '892 & '456 patents as requested
Eligible for TA

2. Project Manager, [illegible] Team 3
Review Support Branch
Date 1/15/04 Date 1/22/04
Initials [illegible] Initials [illegible]

Original Rec'd date 12/31/02
Date Acceptable for Filing 1/2/03 J
Patent Certification (type) II
Date Patent/Exclus.expires 5/14/04
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabled Yes ☒ No ☐
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6/30/03
Date of Office Bio Review 12/19 9/5/03
Date of Labeling Approv. Sum 8/5/03
Date of Sterility Assur. App. 12/1/03
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./NA Minor issued ☐ Date
Comments:

3. Div. Dir./~~Deputy Dir~~.
Chemistry Div. I or II
Comments:
Date 1/22/04
Initials RAC

The CMC section is satisfactory for TA

4. Frank Holcombe **First Generics Only**
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
Date
Initials

N/A. The following ANDAs for this drug product have been tentatively approved: Novex 76-513; Alcon 76-231.

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date 1/23/04
Initials RLW for

RLD = Ocuflox Ophthalmic Solution 0.3%
Allergan Inc. NDA 19-921

6. Peter Rickman
Director, DLPS
Date 1/23/04
Initials RLW for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 6/30/03 (Verified 1/23/04). No OAI alerts noted. Bioequivalence waiver granted under 21 CFR 320.22(b)(4). Pkg product is "AA" to the RLD. Office-level bio endorsed 9/5/03. Labeling found acceptable for TA on 8/5/03. Microbiology/sterility assurance found acceptable 12/1/03. CMC found acceptable 1/2/04. Methods validation is not required - the API and the drug product are compendial.

6. Robert L. West
~~Acting~~ Deputy Director, OGD
Date 1/23/2004
Initials RLW for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: At the time of filing, B+L made paragraph III certifications to the '892 (9/2/03) and '456 (11/4/03) patents. Each patent was subsequently extended by 6 months upon the granting of pediatric exclusivity to Allergan. On 12/31/03, B+L changed the patent certifications to paragraph II, and acknowledged Allergan's pediatric exclusivity.

This ANDA is recommended for tentative approval. Final approval due upon expiration of Allergan's exclusivity on 5/14/04.

7. Gary Buehler
Director, OGD
Date 1/23/04
Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Leader Review Support Branch
Date 1/23/04
Initials [illegible]
NA Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2:15 Time notified of approval by phone 2:30 Time approval letter faxed
FDA Notification:
1/23/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1/23/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File: V:/division/dlps/approvals5.doc

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Tel 813 975 7700
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2.1

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& LOMB

March 12, 2004

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

ORIG AMENDMENT
N/AM

Re: ANDA 76-622: Ofloxacin Ophthalmic Solution, 0.3% (Sterile)
Minor Amendment – Final Approval Requested

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's January 23, 2004 Tentative Approval letter for the above reference ANDA. A copy of the Agency's letter is enclosed in Attachment 1.

Bausch & Lomb requests final approval of ANDA 76-622 pursuant to 21 U.S.C. 355(J)(5)(ii) upon expiry of market exclusivity for the Reference Listed Drug (RLD), Ocuflox Ophthalmic Solution, 0.3%. As indicated by the Orange Book, market exclusivity for the RLD expires May 14, 2004 (Attachment 2)

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 866-2102 or facsimile (813) 975-7757.

Sincerely,

J. B. Hawk -

Joseph B. Hawkins
Director,
Regulatory Affairs

Enclosure

RECEIVED
MAR 15 2004
OGD/CDER

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

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& LOMB

March 16, 2004

ORIG AMENDMENT
N/AF
FPL

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: ANDA 76-622: Ofloxacin Ophthalmic Solution, 0.3% (Sterile)
Final Printed Labeling

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's January 23, 2004 Tentative Approval letter for the above reference ANDA. A copy of the Agency's letter is enclosed in Attachment 1.

Bausch & Lomb submitted a Minor Amendment March 12, 2004, requesting final approval of ANDA 76-622. Twelve copies each of final printed container, carton and package insert labeling are enclosed (Attachment 2) in support of the requested approval. On all labeling, the name of the manufacturer has been changed from Bausch & Lomb Pharmaceuticals, Inc. to Bausch & Lomb, Incorporated. The enclosed labeling has no other changes from that previously reviewed by the Agency.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 866-2102 or facsimile (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Director,
Regulatory Affairs

Enclosure

RECEIVED
MAR 17 2004
OGD/CDER

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH
& LOMB

April 22, 2004

ORIG AMENDMENT

N/AF

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: ANDA 76-622: Ofloxacin Ophthalmic Solution, 0.3% (Sterile)
Telephone Amendment -Final Printed Labeling

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's April 21, 2004 request for modified copies of the container labeling included in our March 16, 2004 submission of Final Printed Labeling for the above reference ANDA.

Twelve copies each of final printed container labeling are enclosed in support of the final approval requested in our March 12, 2004 Minor Amendment.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 866-2102 or facsimile (813) 975-7757.

Sincerely,

JB Hawkins

Joseph B. Hawkins
Director,
Regulatory Affairs

Enclosure

RECEIVED
APR 2 3 2004
OGD / CDER

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-622 Applicant Bausch + Lomb
Drug Ofloxacin Ophthalmic Solution Strength(s) 0.3%

APPROVAL X TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 30 Apr 2004 Initials MJS	Date 5/6/04 for Initials

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)
Patent/Exclusivity Certification: (Yes) No
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes No
Was applicant sued w/in 45 days: Yes No
Has case been settled: Yes No
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No
Type of Letter:
Comments: Both 6924 & 4456 patents have expired. PED ext. to the 4456 patent expires 5/14/2004. Eligible for full Approval on 5/14/2004

Determ. of Involvement? Yes (No)
Pediatric Exclusivity System
RLD = NDA# 19-921
Date Checked Previously granted.
Nothing Submitted
Written request issued
Study Submitted
Date settled:

2. Project Manager, T.J Team 3 Review Support Branch	Date 4/27/04 Initials TJ	Date Initials

Original Rec'd date 12/31/02
Date Acceptable for Filing 1/2/03
Patent Certification (type) I
Date Patent/Exclus.expires 5/14/04
Citizens' Petition/Legal Case Yes ~~No~~
(If YES, attach email from PM to CP coord)
First Generic Yes ~~No~~
Acceptable Bio reviews tabbed ~~Yes~~ No
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending Acceptable OAI
Date of EER Status 6/30/03
Date of Office Bio Review 9/5/03
Date of Labeling Approv. Sum ~~8/5/03~~ 4/28/04
Date of Sterility Assur. App. 12/1/03
Methods Val. Samples Pending Yes No
MV Commitment Rcd. from Firm Yes No
Modified-release dosage form: Yes No
Interim Dissol. Specs in AP Ltr: Yes

Previously reviewed and tentatively approved Date 1/23/04
Previously reviewed and CGMP def./NA Minor issued Date
Comments:

3. Div. Dir./~~Deputy Dir.~~ Chemistry Div. I ~~or II~~ Comments:		Date 5/4/04 Initials IRS

The CMC section remains satisfactory since issuance of the TA letter dated 1/23/04

4. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	**First Generics Only** N/A	Date - Initials -

Multiple ANDAs have been tentatively approved for this drug product.

REVIEWER: FINAL ACTION

5. Gregg Davis
Deputy Dir., DLPS
Date _____
Initials _____

RLD= Ocuflox Ophthalmic Solution 0.3%
Allergan Inc. NDA 19-921

6. Peter Rickman
Director, DLPS
Date 5/6/04 Yes for
Initials PR

Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: Acceptable EES dated 6/30/03 (Verified 5/6/04). No OAI alerts noted. Refer to the administrative sign-off completed at the time of the tentative approval issued on 1/23/04. On March 12, 2004 Bausch+Lomb submitted a major amendment to request final approval effective 5/14/04. B+L submitted updated labeling on 3/16/04 and on 4/22/04. IPL found acceptable for approval 4/28/04. CMC found acceptable for approval 5/4/04. Methods validation is not required.

6. Robert L. West
Deputy Director, OGD
Date 5/13/2004
Initials Robert West

Para.IV Patent Cert: Yes (No); Pending Legal Action: Yes (No); Petition: Yes (No)
Comments: At the time of filing, Bausch+Lomb (B+L) made paragraph III certifications to the '456 and '892 patents listed for Allergan's Ocuflox Ophthalmic Solution. Allergan was subsequently awarded pediatric exclusivity for Ocuflox. The '892 patent and its pediatric extension have expired (3/2/04) the exclusivity attached to the '456 patent is due to expire on May 14, 2004. B+L previously submitted a revised patent certification (to a paragraph II certification) and to acknowledge Allergan's period of pediatric exclusivity.

This ANDA is eligible for full approval on May 14, 2004 (upon the expiration of Allergan's exclusivity).

7. Gary Buehler
Director, OGD
Date 5/14/04
Initials GB
Comments:

First Generic Approval X PD or Clinical for BE Special Scientific or Reg.Issue

8. Project Manager, Team Leader, Review Support Branch
Date 5/14/04
Initials VG

N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
9:24 Time notified of approval by phone 9:27 Time approval letter faxed
FDA Notification:
5/14/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/14/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou6.doc