

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 76-527

Name: Ofloxacin Otic Solution, 0.3%

Sponsor: Apotex Corp.

Approval Date: November 18, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-527

CONTENTS

Reviews / Information Included in this Review
--

Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Reviews	X
Medical Review	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review	
Microbiology Reviews	X
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-527

APPROVAL LETTER

NOV 18 2005

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Kalpesh Shroff
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 28, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ofloxacin Otic Solution, 0.3%.

Reference is also made to your amendments dated September 16, 2003; June 2, and June 10, 2004; and August 11, August 30, October 13, and October 17, 2005.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved. The Division of Bioequivalence has determined your Ofloxacin Otic Solution, 0.3%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Floxin Otic Solution, 0.3%, of Daiichi Pharmaceutical Company, Ltd. (Daiichi).

The listed drug product referenced in your ANDA, Daiichi's Floxin Otic Solution, is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,401,741 (the '741 patent) expires March 27, 2012.

Your ANDA contains a certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '741 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Ofloxacin Otic Solution, 0.3%, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an

action was brought for infringement of the '741 patent before the expiration of 45 days from the date of the notice provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You further informed the agency Apotex Inc. (Apotex) complied with the requirements of Section 505(j)(2)(B) of the Act, and that Daiichi initiated a patent infringement suit against you with respect to the '741 patent in the United States District Court for the District of New Jersey (Daiichi Pharmaceutical Co., Ltd., and Daiichi Pharmaceutical Corporation v. Apotex Inc., Civil Action No. 03 CV 937(WGB)). Although this litigation remains ongoing, the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

With respect to 180-day generic drug exclusivity, the agency has concluded that Apotex was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '741 patent. Therefore, with this approval Apotex is eligible for 180 days of generic drug exclusivity for Ofloxacin Otic Solution, 0.3%. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act,¹ will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

¹ Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Robert L. Buehler", followed by a vertical line and the date "11/18/2005".

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-527
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

Endorsements:

HFD-629/L.Huang/

HFD-623/J.Fan/

HFD-617/T.Vu/

HFD-613/B.Weitzman/

HFD-613/J.Grace/

L Huang 11/17/05

[Signature] 11/15/05

[Signature] 11/16/05

*Robert West
11/18/2005*

V:\FIRMSAM\Apotex\LTRS&REV\76527.ap.DOC
F/T by

APPROVAL

PS 11/10/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-527

LABELING



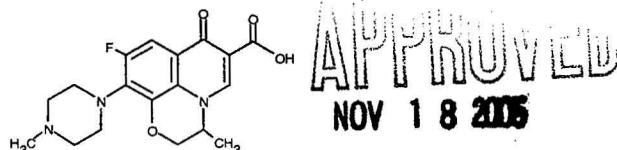
204984

PRESCRIBING INFORMATION

Rx Only
Ofloxacin Otic Solution, 0.3%

DESCRIPTION

Ofloxacin Otic Solution 0.3% is a sterile aqueous anti-infective (anti-bacterial) solution for otic use. Chemically, ofloxacin has three condensed 6-membered rings made up of a fluorinated carboxyquinolone with a benzoxazine ring. The chemical name of ofloxacin is: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7 H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. The empirical formula of ofloxacin is $C_{18}H_{20}FN_3O_4$ and its molecular weight is 361.38. The structural formula is:



Ofloxacin Otic Solution contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), hydrochloric acid, sodium chloride, and water for injection. Additional hydrochloric acid and/or sodium hydroxide may be added to adjust the pH (6.5 ± 0.5).

CLINICAL PHARMACOLOGY

Pharmacokinetics: Drug concentrations in serum (in subjects with tympanostomy tubes and perforated tympanic membranes), in otorrhea, and in mucosa of the middle ear (in subjects with perforated tympanic membranes) were determined following otic administration of ofloxacin solution. In two single-dose studies, mean ofloxacin serum concentrations were low in adult patients with tympanostomy tubes, with and without otorrhea, after otic administration of a 0.3% solution (4.1 ng/mL (n=3) and 5.4 ng/mL (n=5), respectively). In adults with perforated tympanic membranes, the maximum serum drug level of ofloxacin detected was 10 ng/mL after administration of a 0.3% solution. Ofloxacin was detectable in the middle ear mucosa of some adult subjects with perforated tympanic membranes (11 of 16 subjects). The variability of ofloxacin concentration in middle ear mucosa was high. The concentrations ranged from 1.2 to 602 µg/g after otic administration of a 0.3% solution. Ofloxacin was present in high concentrations in otorrhea (389-2850 µg/g, n=13) 30 minutes after otic administration of a 0.3% solution in subjects with chronic suppurative otitis media and perforated tympanic membranes. However, the measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

Microbiology: Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription. 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 isolates of the following microorganisms, both *in vitro* and clinically in otic infections as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative gram-positive microorganisms:

Staphylococcus aureus
Streptococcus pneumoniae

Aerobic and facultative gram-negative microorganisms:

Escherichia coli
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

INDICATIONS AND USAGE

Ofloxacin Otic Solution 0.3% is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

CONTRAINDICATIONS

Ofloxacin Otic Solution 0.3% 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 OPHTHALMIC USE.

NOT FOR INJECTION.

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. If an allergic reaction to ofloxacin is suspected, stop 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-infective preparations, prolonged use may result in over-growth of nonsusceptible organisms, including fungi. If the infection is not improved after one week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for one month.

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

Information for Patients: Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. 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.

Acute Otitis Media and Chronic Suppurative Otitis Media

Prior to administration of Ofloxacin Otic Solution, the solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions: Specific drug interaction studies have not been conducted with Ofloxacin Otic Solution.

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, the sister chromatid exchange assay (Chinese hamster and human cell lines), the unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or the mouse micronucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin did not affect male or female reproductive performance at oral doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area, assuming total absorption of ofloxacin from the ear of a patient treated with Ofloxacin Otic Solution twice per day.

Pregnancy

Teratogenic Effects: Pregnancy Category C. Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

These dosages resulted in decreased fetal body weights 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.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses.

Nonteratogenic Effects: Additional studies in the rat demonstrated that doses up to 360 mg/kg/day during late gestation had no adverse effects 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 Otic 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 otic 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 efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- one year and older: acute otitis media with tympanostomy tubes
- twelve years and older: chronic suppurative otitis media with perforated tympanic membranes.

Safety and efficacy in pediatric patients below these ages have not been established.

Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product.

No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters.

Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for one month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

ADVERSE REACTIONS

In twice daily dosing studies, the following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing, and otorrhagia.

Subjects with Acute Otitis Media with Tympanostomy Tubes (AOM TT) and Subjects with Chronic Suppurative Otitis Media (CSOM) with Perforated Tympanic Membranes

In phase III clinical trials which formed the basis for approval, the following treatment-related adverse events occurred in 1% or more of the 656 subjects with non-intact tympanic membranes in AOM TT or CSOM treated twice-daily with ofloxacin otic solution:

Adverse Event	Frequency (n=656)
Taste Perversion	7%
Earache	1%
Pruritus	1%
Paraesthesia	1%
Rash	1%
Dizziness	1%

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

Post-marketing Adverse Events

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

DOSAGE AND ADMINISTRATION

Acute Otitis Media in Pediatric Patients with Tympanostomy Tubes: The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from one to 12 years old) with tympanostomy tubes is:

Five drops (0.25 mL, 0.75 mg ofloxacin) instilled into the affected ear twice daily for ten days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

Chronic Suppurative Otitis Media with Perforated Tympanic Membranes: The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years and older is:

Ten drops (0.5 mL, 1.5 mg ofloxacin) instilled into the affected ear twice daily for fourteen days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, before instilling the drops. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

HOW SUPPLIED

Ofloxacin Otic Solution 0.3% is supplied in bottles containing 5 mL and 10 mL. The NDC codes are: 60505-0363-1 Ofloxacin Otic Solution 5 mL; 60505-0363-2 Ofloxacin Otic Solution 10 mL.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature].

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

204984

May 2004

PATIENT INFORMATION
Rx Only
Ofloxacin Otic Solution, 0.3%

IMPORTANT PATIENT INFORMATION AND INSTRUCTIONS. READ BEFORE USE.

What is Ofloxacin Otic Solution?

Ofloxacin Otic Solution is an antibiotic in a sterile solution used to treat ear infections caused by certain bacteria found in:

- patients (12 years and older) who have a middle ear infection and have a hole in the eardrum
- pediatric patients (between 1 and 12 years of age) who have a middle ear infection and have a tube in the eardrum

Middle Ear Infection: A middle ear infection is a bacterial infection behind the eardrum. People with a hole or a tube in the eardrum may notice a discharge (fluid draining) in the ear canal.

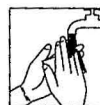
Who should NOT use Ofloxacin Otic Solution?

- Do not use this product if allergic to ofloxacin or to other quinolone antibiotics.
- Do not give this product to pediatric patients who:
 - have a middle ear infection and have a tube in the eardrum and are less than one year of age because no data were collected from this population
 - have a middle ear infection and have a hole in the eardrum and are less than 12 years of age because no data were collected from this population

How should Ofloxacin Otic Solution be given?

1. Wash hands

The person giving Ofloxacin Otic Solution should wash his/her hands with soap and water.



2. Clean ear & warm bottle

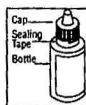
Gently clean any discharge that can be removed easily from the outer ear. **DO NOT INSERT ANY OBJECT OR SWAB INTO THE EAR CANAL.**

Hold the bottle of Ofloxacin Otic Solution in the hand for one or two minutes to warm the solution.



Before using the medication for the first time, be sure the white plastic sealing tape between the bottle and the cap is unbroken.

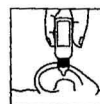
To break the seal and open the bottle, unscrew the cap by turning as indicated by the arrow.



3. Add drops

For a **Middle Ear Infection:**

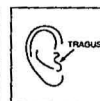
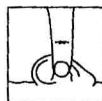
The person receiving Ofloxacin Otic Solution should lie on his/her side with the infected ear up. Patients (12 and older) should have **10 drops** of Ofloxacin Otic Solution put into the infected ear. Pediatric patients under 12 should have **5 drops** put into the infected ear. The tip of the bottle should not touch the fingers or the ear or any other surfaces.



4. Press ear or pull ear

For a **Middle Ear Infection:**

While the person receiving Ofloxacin Otic Solution lies on his/her side, the person giving the drops should gently press the **TRAGUS** (see diagram) 4 times in a pumping motion. This will allow the drops to pass through the hole or tube in the eardrum and into the middle ear.



5. Stay on side

The person who received the ear drops should remain on his/her side for at least 5 minutes.



Repeat Steps 2-5 for the other ear if both ears are infected.

How often should Ofloxacin Otic Solution be given?

In patients with a Middle Ear Infection, Ofloxacin Otic Solution ear drops should be given 2 times each day (about 12 hours apart, for example 8 AM and 8 PM) in each infected ear unless the doctor has instructed otherwise. The best times to use the ear drops are in the morning and at night.

It is very important to use the ear drops for as long as the doctor has instructed, **even if the symptoms improve**. If Ofloxacin Otic Solution ear drops are not used for as long as the doctor has instructed, the infection may be more likely to return.

What if a dose is missed?

In patients with a Middle Ear Infection, if a dose of Ofloxacin Otic Solution is missed, it should be given as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule.

Do not use a double dose unless the doctor has instructed you to do so. If the infection is not improved after one week, you should consult your doctor. If you have two or more episodes of drainage within six months, it is recommended that you see your doctor for further evaluation.

What activities should be avoided while using Ofloxacin Otic Solution?

It is important that the infected ear(s) remain clean and dry. When bathing, avoid getting the infected ear(s) wet. Avoid swimming unless the doctor has instructed otherwise.

What are some of the possible side effects of Ofloxacin Otic Solution?

During the testing of Ofloxacin Otic Solution in external ear infections, the most common side effect was discomfort upon application which happened in 7% of patients. If the pain is severe, the medication should be stopped and you should contact your doctor. Other side effects were: itching (1%), earache (0.8%), and dizziness (0.4%).

During testing in middle ear infections, the most common side effect was a bitter taste which happened in 7% of patients with a middle ear infection. This may occur when some of the drops pass from the middle ear to the back of the mouth. This side effect is not serious and there is no need to stop the medicine if this should happen. Other side effects which were found in 1% of the patients were: earache, itching, abnormal sensation, rash and dizziness.

Call your doctor about these or other side effects if they occur.

If a rash or an allergic reaction to Ofloxacin Otic Solution occurs, stop using the product and contact your doctor.

DO NOT TAKE OFLOXACIN OTIC SOLUTION BY MOUTH.

If Ofloxacin Otic Solution is accidentally swallowed or overdose occurs, call the doctor immediately. This medicine is available only with a doctor's prescription. Use only as directed. Do not use this medicine if outdated.

If you wish to learn more about Ofloxacin Otic Solution ask the doctor or pharmacist. Complete Prescribing Information is available from your doctor or pharmacist upon request.

HOW SUPPLIED

Bottles containing 5 mL and 10 mL.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature].

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

204984

May 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-527

LABELING REVIEWS

APPROVAL SUMMARY #2

Supersedes Approval Summary from April 14 2003 Submission

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

ANDA Number: 76- 527

Date of Submission: **June 2, 2004**

Applicant's Name: Apotex Inc.

Established Name: Ofloxacin Otic 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) – Satisfactory as of **June 2, 2004** paper submission [Vol 2.1; Code # 204980]
- **Container Labels:** (10 mL) – Satisfactory as of **June 2, 2004** paper submission [Vol 2.1; Code # 205271]
- **Carton Labeling:** (5 mL) – Satisfactory as of **June 2, 2004** paper submission [Vol 2.1; Code # 204982]
- **Carton Labeling:** (10 mL) – Satisfactory as of **June 2, 2004** paper submission [Vol 2.1; Code # 205285]
- **Professional Package Insert Labeling:** Satisfactory as of **June 2, 2004** paper submission. [Vol 2.1; Revised 04/02 ; Code # 204984]
- **Medication Guide:** Satisfactory as of **June 2, 2004** paper submission. [Vol 2.1; Revised 05/04; Code # 204984]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Floxin Otic Solution, 0.3%
- NDA Number: 20-799
- NDA Drug Name: Ofloxacin Otic Solution, 0.3%
- NDA Firm: Daiichi
- Date of Approval of NDA Insert: 20-799/S-006: Approved September 30, 2003
- 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 20-799

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5401741	March 27, 2012	U-407	METHOD OF TREATING OTOPATHY	PIV	NONE

Exclusivity-Data – NDA 20-799

Code	Reference	Expiration	Labeling Impact
(b) (4)			

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			
Is the scoring configuration different than the RLD?			X
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	
		X	

Do any of the inactives differ in concentration for this route of administration?			
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		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the reference listed drug Floxin Otic Solution by Daiichi, (NDA 20-799/S-006: Approved September 30, 2003). This supplement provides for (b) (4)

Please note that supplement S-012 was approved October 7, 2003. This supplement incorporates an additional adverse event heading and an adverse event noted in spontaneous post-marketing reports. However, when S-12 was compared to S-006 the insert labeling for S-012 the same as S-006, therefore the review was based on S-006. In addition, S-016 was approved May 4, 2005, which provides for an additional word "transient" in front of the adverse event "loss of hearing". This does not effect the labeling for this ANDA, since this information is part of (b) (4)

2. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

[Vol. A1.1 Section VII pg. 86]

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-799

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5401741	March 27, 2012	U-407	METHOD OF TREATING OTOPATHY	PIV	NONE

Exclusivity-Data – NDA 20-799

Code	Reference	Expiration	Labeling Impact
(b) (4)			

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: NONE
- RLD: Stored at 15° to 25°C (59° to 77°F).
- ANDA: (b) (4)

5. **DISPENSING STATEMENT COMPARISON**

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

6. **PACKAGE CONFIGURATION**

- RLD: Packaged in plastic dropper bottles containing 5 ml's and 10 ml's.
- ANDA: Packaged in 5 ml. and 10 ml (b) (4) bottle (b) (4)

[Vol. A1.2 pg. 315]

7. **CONTAINER/CLOSURE**

- Packaged into 5 ml and 10 ml (b) (4) bottle (b) (4)

8. **FINISHED DOSAGE FORM**

- RLD: Clear, yellowish solution
- ANDA: A clear, slightly yellow solution supplied in 5 ml and 10 ml (b) (4) bottles.

[Vol. A1.2 pg. 432]

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Manufactured by: Apotex Inc
Toronto, Ontario
Canada M9L 1T9

Date of Review:

Date of Submission: June 2, 2004

Primary Reviewer: Beverly Weitzman

Date: 7/28/2005

Team Leader: J. Grace

Date: 7/28/2005

cc:

ANDA: 76-527
DUP/DIVISION FILE
HFD-613/Jgrace (no cc)

Review

APPROVAL SUMMARY

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

ANDA Number: 76- 527

Date of Submission: April 14, 2003

Applicant's Name: Novex Pharma

Established Name: Ofloxacin Otic 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 as of April 14, 2003 submission [Vol 2.1; Code # 204980 and 205271, respectively]

Carton Labeling: (5 mL and 10 mL) – Satisfactory as of April 14, 2003 submission [Vol 2.1; Code # 204982 and 205285, respectively]

Professional Package Insert Labeling: Satisfactory as of April 14, 2003 submission. [Vol 2.1; Revised 04/02 ; Code # 204984]

Medication Guide: Satisfactory as of April 14, 2003 submission. [Vol 2.1; Revised 04/02; Code # 204984]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Floxin Otic Solution, 0.3%
- NDA Number: 20-799
- NDA Drug Name: Ofloxacin Otic Solution, 0.3%
- NDA Firm: Daiichi
- Date of Approval of NDA Insert: Approved December 16, 1997
- 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 20-799

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5401741	March 27, 2012	U-407	METHOD OF TREATING OTOPATHY	PIV	NONE

Exclusivity Data– NDA 20-799

Code	Reference	Expiration	Labeling Impact
NONE	There is no unexpired exclusivity for this product.		

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:** Does the firms stability data support their storage temperature "Store at (b) (4) ?

FOR THE RECORD:

1. MODEL LABELING

This review was based on the October 15, 1999 labeling taken from the PDR for Floxin Otic Solution by Daiichi, NDA 20-799. The approved labeling was December 16, 1997.

2. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
[Vol. A1.1 Section VII pg. 86]

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-799

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5401741	March 27, 2012	U-407	METHOD OF TREATING OTOPATHY	PIV	NONE

Exclusivity-Data – NDA 20-799

Code	Reference	Expiration	Labeling Impact
NONE	THERE IS NO UNEXPIRED EXCLUSIVITY FOR THIS PRODUCT IN THE ORANGE BOOK DATABASE	N/A	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: NONE
- RLD: Stored at 15° to 25°C (59° to 77°F).
- ANDA: (b) (4)

5. DISPENSING STATEMENT COMPARISON

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

6. PACKAGE CONFIGURATION

- RLD: Packaged in plastic dropper bottles containing 5 ml's and 10 ml's.
- ANDA: Packaged in 5 ml, and 10 ml in (b) (4) bottle (b) (4)

[Vol. A1.2 pg. 315]

7. CONTAINER/CLOSURE

- Packaged into 5 ml and 10 ml (b) (4) bottle (b) (4)

8. FINISHED DOSAGE FORM

- RLD: Clear, yellowish solution
 - ANDA: A clear, slightly yellow solution supplied in 5 ml and 10 m (b) (4) bottles.
- [Vol. A1.2 pg. 432]

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Manufactured by: Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
[Vol. A1.1 pg. 158]

Date of Review: 03/11/03

Date of Submission: April 14, 2003

Primary Reviewer: Beverly Weitzman

Date: 6/5/2003

Team Leader: John J. Grace

Date: 6/10/2003

cc:

ANDA: 76-527
DUP/DIVISION FILE
HFD-613/Jgrace (no cc)
V:\FirmsNZ\Novex\LTRS&REV\76527NA1.L.doc
Review

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

ANDA Number: 76- 527

Date of Submission: October 7, 2002

Applicant's Name: Novex Pharma

Established Name: Ofloxacin Otic Solution USP, 0.3%

Labeling Deficiencies:

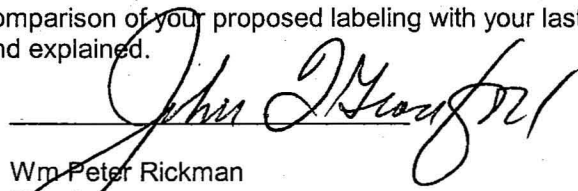
1. **CONTAINER** (5 ml and 10 ml)
Please include the active and inactive ingredients on your container label.
2. **CARTON** (5 ml and 10 ml) - Satisfactory in draft.
3. **INSERT** – Satisfactory in draft.
4. **MEDICATION GUIDE** - Satisfactory in draft.

Please revise your container labels as instructed above, then submit in draft for a tentative approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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: Does the firms stability data support their storage temperature "Store at (b) (4) ?

FOR THE RECORD:

1. MODEL LABELING

This review was based on the October 15, 1999 labeling taken from the PDR for Floxin Otic Solution by Daiichi, NDA 20-799. The approved labeling was December 16, 1997.

2. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
[Vol. A1.1 Section VII pg. 86]

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-921

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5401714	March 27, 2012	U-407	METHOD OF TREATING OTOPATHY	PIV	NONE

Exclusivity-Data – NDA 19-921

Code	Reference	Expiration	Labeling Impact
NONE	THERE IS NO UNEXPIRED EXCLUSIVITY FOR THIS PRODUCT IN THE ORANGE BOOK DATABASE	N/A	NONE

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: NONE
- RLD: Stored at 15° to 25°C (59° to 77°F).
- ANDA: Store at (b) (4)

5. DISPENSING STATEMENT COMPARISON

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

6. PACKAGE CONFIGURATION

- RLD: Packaged in plastic dropper bottles containing 5 ml's and 10 ml's.
- ANDA: Packaged in 5 ml, and 10 ml in (b) (4) bottle (b) (4)

[Vol. A1.2 pg. 315]

7. CONTAINER/CLOSURE

- Packaged into 5 ml and 10 ml (b) (4) bottle (b) (4)

8. FINISHED DOSAGE FORM

- RLD: Clear, yellowish solution
 - ANDA: A clear, slightly yellow solution supplied in 5 ml and 10 ml (b) (4) bottles.
- [Vol. A1.2 pg. 432]

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Manufactured by: Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
[Vol. A1.1 pg. 158]

Date of Review: 03/11/03

Date of Submission: October 7, 2002

Primary Reviewer: Beverly Weitzman Date: 3/12/03

Team Leader: *John D. Grace* Date: 3/12/2003

cc:

ANDA: 76-527
DUP/DIVISION FILE
HPD-613/Jgrace (no cc)
V:\FirmsNZ\Novex\LTRS&REV\76527NA1.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-527

CHEMISTRY REVIEWS

#3

ANDA 76-527

Ofloxacin Otic Solution, 0.3%

Novex Pharma

Liang-Lii Huang, Ph.D.

DC1/OGD

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary.....	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative.....	10
A. Reviewer's Signature	10
B. Endorsement Block	10
C. CC Block.....	10
Chemistry Assessment	11
20. COMPONENTS AND COMPOSITION	11
21. FACILITIES	12
22. SYNTHESIS	12
23. RAW MATERIAL CONTROLS	12
A. Drug Substance(s).....	12
B. Inactive Ingredients	14
24. OTHER FIRM(s)	14
25. MANUFACTURING AND PROCESSING	14
26. CONTAINER	14

27. PACKAGING AND LABELING	14
28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM)	14
29. STABILITY	17
30. MICROBIOLOGY	20
31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS	20
32. LABELING.....	20
33. ESTABLISHMENT INSPECTION	20
34. BIOEQUIVALENCE	20
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:...	20

~~Error! Bookmark not defined.~~



Chemistry Review Data Sheet

1. ANDA 76-527

2. REVIEW # 3

3. REVIEW DATE:

10/7/05; revised 10/14/05

4. REVIEWER:

Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission	Date
Original	October 28, 2002
Acceptable for filing	November 4, 2002
New correspondence	December 10, 2002
Patent amendment	February 25, 2003
Minor amendment	February 27, 2003
Labeling amendment	April 10, 2003
Patent amendment	May 01, 2003
Microbiology amendment	July 7, 2003
Minor amendment	August 11, 2005
Telephone amendment	October 13, 2005
Telephone amendment	October 17, 2005



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name	Novex Pharma
Address	380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Telephone	(905) 508-2562
FAX	905-884-0357
U.S. Agent	Apotex Corp.
Address	2400 North Commerce Parkway, Suite 400 Weston, FL 33326
Telephone	954-349-4217
Fax	954-349-4266
Contact person	Kalpesh Shroff

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN):
Ofloxacin Otic Solution, 0.3%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Floxin® Otic (ofloxacin otic solution) 0.3%
NDA #020799, held by Daiichi

Patent certification: Paragraph IV certification (p.11)

Novex Pharma hereby certifies that, in its opinion and to the best of its knowledge, US Patent # 5401741, expiring on March 27, 2012 is invalid and will not be infringed by the manufacture, use, or sale of the ofloxacin product for which this application is submitted.

Exclusivity

There is no unexpired exclusivity for this product. (p10)

10. PHARMACOL. CATEGORY:

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

11. DOSAGE FORM:

Chemistry Review Data Sheet

Solution/drops

12. STRENGTH/POTENCY:

0.3%

13. ROUTE OF ADMINISTRATION:

otic

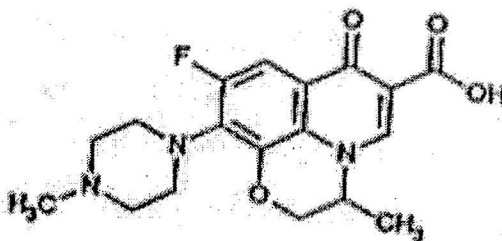
14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):☐ SPOTS product – Form Completed☒ Not a SPOTS product

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

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

CAS: 82419-36-1

Molecular weight: 361.4





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate	10/18/05	Liang-Lii Huang, Ph.D.
				4			
				4			

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
None		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	10/17/03	Lisa Shelton
EES	Acceptable	1/22/03	
Methods Validation	Acceptable	10/18/04	Southeast Regional Lab (R. Roberts)
Labeling	acceptable	6/11/03	B. Weitzman
Bioequivalence	Acceptable	3/25/03	M. Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable.

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)

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

Ofloxacin is a fluorinated 4-quinolone which differs from other fluorinated 4-quinolones in that there is a six member (pyridobenzoxazine) ring from position 1 to 8 of the basic ring structure.

Ofloxacin Otic Solution, 0.3% is a sterile product. The bulk otic solution is (b) (4)

The ofloxacin drug substance is a white to yellowish crystalline powder. It melts at about 255°C with decomposition. It has a pKa (b) (4) It is poorly soluble in water or ethanol.

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

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

MDD = (b) (4) /day
 For DS, IT = (b) (4) %, QT (b) (4) %
 For DP, IT = (b) (4) %, QT (b) (4) %

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable.

III. Administrative**A. Reviewer's Signature**

Liang-Lii Huang, Ph.D.

B. Endorsement Block

HFD 627 / Liang-Lii Huang, Ph.D./10/7/05;10/20/05

HFD 627 /James Fan, TL /10/7/05;10/20/05

HFD 617/ Ann Vu, PM/10/20/05

L Huang 11/15/05

C. CC Block

ANDA 76-527

ANDA DUP

DIV FILE

Field Copy

15 pages following this page are withheld as b4

#2

ANDA 76-527

Ofloxacin Otic Solution, 0.3%

Novex Pharma

Liang-Lii Huang, Ph.D.

DC1/OGD

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary.....	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative.....	10
A. Reviewer's Signature	10
B. Endorsement Block	10
C. CC Block.....	10
Chemistry Assessment	11
20. COMPONENTS AND COMPOSITION	11
21. FACILITIES	12
22. SYNTHESIS	12
23. RAW MATERIAL CONTROLS	12
A. Drug Substance(s).....	12
B. Inactive Ingredients	14
24. OTHER FIRM(s)	14
25. MANUFACTURING AND PROCESSING	14
26. CONTAINER	15



CHEMISTRY REVIEW



27. PACKAGING AND LABELING	15
28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM)	15
29. STABILITY	19
30. MICROBIOLOGY	22
31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS	22
32. LABELING.....	22
33. ESTABLISHMENT INSPECTION	22
34. BIOEQUIVALENCE	22
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:....	22



Chemistry Review Data Sheet

1. ANDA 76-527

2. REVIEW # 2

3. REVIEW DATE:

8/21/03

4. REVIEWER:

Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission	Date
Original	October 28, 2002
Acceptable for filing	November 4, 2002
New correspondence	December 10, 2002
Patent amendment	February 25, 2003
Minor amendment	February 27, 2003
Labeling amendment	April 10, 2003
Patent amendment	May 01, 2003
Microbiology amendment	July 7, 2003

7. NAME & ADDRESS OF APPLICANT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Name	Novex Pharma
Address	380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Telephone	(905) 508-2562
FAX	905-884-0357
U.S. Agent	Apotex Corp.
Address	50 Lakeview Parkway, Suite 127 Vernon Hills, IL 60061
Telephone	847-573-9999
Fax	847-573-1001
Contact person	Marcy Macdonald

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN):
Ofloxacin Otic Solution, 0.3%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Floxin® Otic (ofloxacin otic solution) 0.3%
NDA #020799, held by Daiichi

Patent certification: Paragraph IV certification (p.11)

Novex Pharma hereby certifies that, in its opinion and to the best of its knowledge, US Patent # 5401741, expiring on March 27, 2012 is invalid and will not be infringed by the manufacture, use, or sale of the ofloxacin product for which this application is submitted.
Exclusivity

There is no unexpired exclusivity for this product. (p10)

10. PHARMACOL. CATEGORY:

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: 1) (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

11. DOSAGE FORM:

Solution/drops

12. STRENGTH/POTENCY:

Chemistry Review Data Sheet

0.3%

13. ROUTE OF ADMINISTRATION:

otic

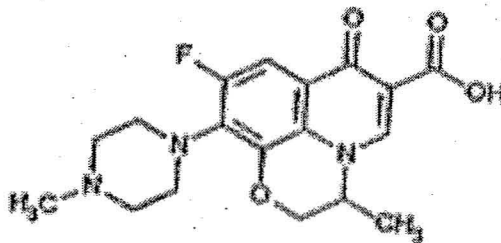
14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):☐ SPOTS product – Form Completed☒ Not a SPOTS product

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

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

CAS: 82419-36-1

Molecular weight: 361.4





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	5/20/03	R.Randad
				4			
				4			

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
None		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Has deficiencies	8/29/03	Lisa Shelton
EES	Acceptable	1/22/03	
Methods Validation	MV requested for DP	1/7/03	
Labeling	acceptable	6/11/03	B. Weitzman
Bioequivalence	Acceptable	3/25/03	M. Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

It is recommended that this application be not approvable at this time.
CMC is OK. Micro is deficient.

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)

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: 1) (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

Ofloxacin is a fluorinated 4-quinolone which differs from other fluorinated 4-quinolones in that there is a six member (pyridobenzoxazine) ring from position 1 to 8 of the basic ring structure.

Ofloxacin Otic Solution, 0.3% is a sterile product. The bulk otic solution is (b) (4)

The ofloxacin drug substance is a white to yellowish crystalline powder. It melts at about 255°C with decomposition. It has a pKa (b) (4) It is poorly soluble in water or ethanol.

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

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: 1) (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

It is recommended this application is not approvable. Micro is deficient.

III. Administrative**A. Reviewer's Signature**

Liang-Lii Huang, Ph.D.

B. Endorsement Block

HFD 627 / Liang-Lii Huang, Ph.D./8/21/03

HFD 627 /James Fan /8/21/03

C. CC Block

15 pages following this page are withheld as
b4

#1

ANDA 76-527

Ofloxacin Otic Solution, 0.3%

Novex Pharma

Liang-Lii Huang, Ph.D.

DC1/OGD

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary.....	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative.....	10
A. Reviewer's Signature	10
B. Endorsement Block	10
C. CC Block.....	10
Chemistry Assessment	11
20. COMPONENTS AND COMPOSITION	11
21. FACILITIES	12
22. SYNTHESIS	12
23. RAW MATERIAL CONTROLS	12
A. Drug Substance(s).....	12
B. Inactive Ingredients	13
24. OTHER FIRM(s)	14
25. MANUFACTURING AND PROCESSING	14
26. CONTAINER	16



CHEMISTRY REVIEW



27. PACKAGING AND LABELING	17
28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM)	17
29. STABILITY	20
30. MICROBIOLOGY	22
31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS	22
32. LABELING.....	22
33. ESTABLISHMENT INSPECTION	22
34. BIOEQUIVALENCE	23
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: ...	23
36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT	24



Chemistry Review Data Sheet

1. ANDA 76-527

2. REVIEW # 1

3. REVIEW DATE:
1/3/03

4. REVIEWER:
Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission	Date
Original	October 28, 2002
Acceptable for filing	November 4, 2002
New correspondence	December 10, 2002

7. NAME & ADDRESS OF APPLICANT:

Name	Novex Pharma
Address	380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Telephone	(905) 508-2562



CHEMISTRY REVIEW



Chemistry Review Data Sheet

FAX	905-884-0357
U.S. Agent	Apotex Corp.
Address	50 Lakeview Parkway, Suite 127 Vernon Hills, IL 60061
Telephone	847-573-9999
Fax	847-573-1001
Contact person	Marcy Macdonald

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN):
Ofloxacin Otic Solution, 0.3%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Floxin® Otic (ofloxacin otic solution) 0.3%
NDA #020799, held by Daiichi

Patent certification: Paragraph IV certification (p.11)
Novex Pharma hereby certifies that, in its opinion and to the best of its knowledge, US Patent # 5401741, expiring on March 27, 2012 is invalid and will not be infringed by the manufacture, use, or sale of the ofloxacin product for which this application is submitted.
Exclusivity
There is no unexpired exclusivity for this product. (p10)

10. PHARMACOL. CATEGORY:

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: 1) (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

11. DOSAGE FORM:

Solution/drops

12. STRENGTH/POTENCY:

0.3%

13. ROUTE OF ADMINISTRATION:

otic

14. Rx/OTC DISPENSED: X Rx OTC

Chemistry Review Data Sheet

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

_____ SPOTS product – Form Completed

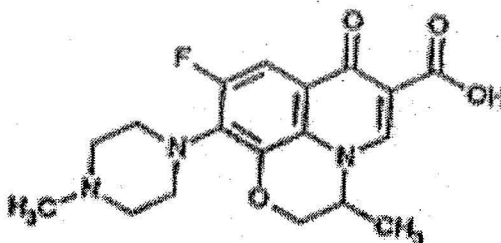
 X Not a SPOTS product

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

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

CAS: 82419-36-1

Molecular weight: 361.4





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	10/16/01	R.Sood, Ph.D.
				4			
				4			

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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending review		
EES	Pending		
Methods Validation	MV requested for DP	1/7/03	
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		



The Chemistry Review for ANDA 76-527

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

It is recommended that this application be not approvable at this time.

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)

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: 1) (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.

Ofloxacin is a fluorinated 4-quinolone which differs from other fluorinated 4-quinolones in that there is a six member (pyridobenzoxazine) ring from position 1 to 8 of the basic ring structure.

Ofloxacin Otic Solution, 0.3% is a sterile product. The bulk otic solution is (b) (4)

The ofloxacin drug substance is a white to yellowish crystalline powder. It melts at about 255°C with decomposition. It has a pKa (b) (4) It is poorly soluble in water or ethanol.

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

It is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms for the following conditions: 1) (b) (4) 2) chronic suppurative otitis media, 3) acute otitis media.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	10/16/01	R.Sood, Ph.D.
				4			
				4			

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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending review		
EES	Pending		
Methods Validation	MV requested for DP	1/7/03	
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

19. ORDER OF REVIEW

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

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

It is not approvable due to the deficiencies found in the following areas.

1.) drug substance, 2.) Method validation for the drug substance, 3.) Drug product, and 4.) Stability including the limit of the weight loss.

III. Administrative**A. Reviewer's Signature**

Liang-Lii Huang, Ph.D.

B. Endorsement Block

HFD 627 / Liang-Lii Huang, Ph.D./1/14/03 *L. Huang 1/16/03*
HFD 627 /James Fan /1/15/03 *James Fan 1/18/07*

C. CC Block

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-527

BIOEQUIVALENCE REVIEWS

MAR 25 2003

Ofloxacin Otic Solution, 0.3%
ANDA #76-527
Reviewer: Moheb H. Makary
W. 76527WAI1002.doc

Novex Pharma
Richmond Hill, Canada
Submission Date:
October 28, 2002

REVIEW OF A WAIVER REQUEST

I. Background

The firm has requested a waiver of an *in vivo* bioequivalence study requirement for its proposed product, Ofloxacin Otic Solution, 0.3%. The RLD is Floxin^R (ofloxacin otic solution), 0.3%, manufactured by Parkdale Pharmaceuticals, Inc. for Daiichi Pharmaceutical Corporation.

The test and the reference products are both ready-to-use sterile aqueous anti-infective solutions for otic use.

II. Formulation comparison

The test and reference formulations are compared as shown below:

Ingredients	Floxin ^R (ofloxacin otic solution) 0.3%* g/L	Ofloxacin Otic Solution, 0.3%, g/L
Ofloxacin	3.0	3.0
Benzalkonium Chloride	0.025	(b) (4)
Sodium Chloride	9.0 (0.9%)	
Sodium Hydroxide	pH adjustment (6.5+0.5)	
Hydrochloric Acid	pH adjustment (6.5+0.5)	
Water for Injection, USP/EP	(b) (4)	

*PDR, 2003 (FLOXIN[®] Otic contains 0.3% (3mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5.)

III. Comments

1. The test product, Ofloxacin Otic Solution, 0.3%, contains the same active and inactive ingredients in the same concentration and dosage form as the reference product, Floxin^R (ofloxacin otic solution) 0.3%.

2. The test product qualifies for a waiver of *in vivo* bioequivalence study under 21 CFR 320.22 (b) (1). The test product (i) is an otic solution and (ii) contains the same active and inactive ingredients in the same concentration as the RLD.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Novex Pharma, demonstrates that Ofloxacin Otic Solution, 0.3%, falls under 21 CFR section 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study requirement for the test product is granted. The Division of Bioequivalence deems the test product, Ofloxacin Otic Solution, 0.3%, bioequivalent to the reference product, Floxin^R (ofloxacin otic solution), 0.3%, manufactured for Daiichi Pharmaceutical Corporation.

The firm should be informed of the above recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 3/24/03

RD INITIALLED

FT INITIALLED GJP SINGH

GJP Singh

Date: 3-24-03

Concur:

Dale P. Conner
Dale P. Conner, Pharm.D.

Date: 3/25/03

Director

Division of Bioequivalence

Mmakary/3-14-03, 3-24-03, 76527STA0203.doc

cc: ANDA #76-527, original, HFD-658 (Makary), Drug File,
Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-527

APPLICANT: Novex Pharma

DRUG PRODUCT: Ofloxacin Otic Solution, 0.3%

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,



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

CC: ANDA #76-527
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader GJP Singh

V:\FIRMSNZ\NOVEX\LTRS&REV\76527WAI1002.doc
Printed in final on 03/24/03

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary *MM*
HFD-658/ Bio team Leader GJP Singh *Cops 3-24-03*
HFD-650/ D. Conner *DC 3/25/03*

BIOEQUIVALENCY - ACCEPTABLE submission date: 10-28-02

1. Waiver (WAI) Strengths: 0.3%
Outcome: AC

Outcome Decisions: **AC** - Acceptable

201

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # :76-527

SPONSOR : Novex Pharma

DRUG AND DOSAGE FORM : Ofloxacin Otic Solution, 0.3%

STRENGTH(S) : 0.3%

TYPES OF STUDIES : Waiver

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : Waiver is granted.

DSI INSPECTION STATUS

Inspection needed: YES / <u>NO</u>	Inspection status:	Inspection results:
First Generic <u>No</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM

DATE : 3/24/03

TEAM LEADER : GJP SINGH, Ph.D. BRANCH : III

INITIAL : Gargopal Singh

DATE : 3-24-03

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC

DATE : 3/25/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-527

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

Review for HFD-620

October 17, 2003

ANDA: 76-527

Drug Product Name

Proprietary: N/A

Non-proprietary: Ofloxacin Otic Solution 0.3%

Drug Product Classification: N/A

Review Number: #3

Subject of this Review

Submission Date: September 16, 2003

Receipt Date: September 17, 2003

Consult Date: N/A

Date Assigned for Review: September 25, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): July 8, 2003

Date(s) of Previous Micro Review(s): August 29, 2003

Applicant/Sponsor

Name: Novex Pharma

**Address: 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada
L4C 5H2**

U.S. Agent

Name: Apotex Corp.

Address: 616 Heathrow Drive, Lincolnshire, IL 60069

Representative: Marcy MacDonald & Gina Sirianni, Reg. Affairs

Telephone: 847-279-7740 & 905-884-0357

Name of Reviewer: Lisa S.G. Shelton

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:**
Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile solution/drops, Otic, 0.3%, packaged in 5 mL and 10 mL (b) (4) bottles (b) (4)
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Antibacterial - Quinolones
- B. SUPPORTING/RELATED DOCUMENTS:**
(b) (4)
- C. REMARKS:** None.

filename: V:\MICROREV\76-527a2.doc

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 manufactured under (b) (4)

[REDACTED]

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies –

The safety risk is considered minimal.

III. Administrative

A. Reviewer's Signature Lisa S.G. Shelton

B. Endorsement Block

Microbiologist, Lisa S.G. Shelton, Ph.D. *10/17/03*
Microbiology Team Leader, Neal J. Sweeney, Ph.D.

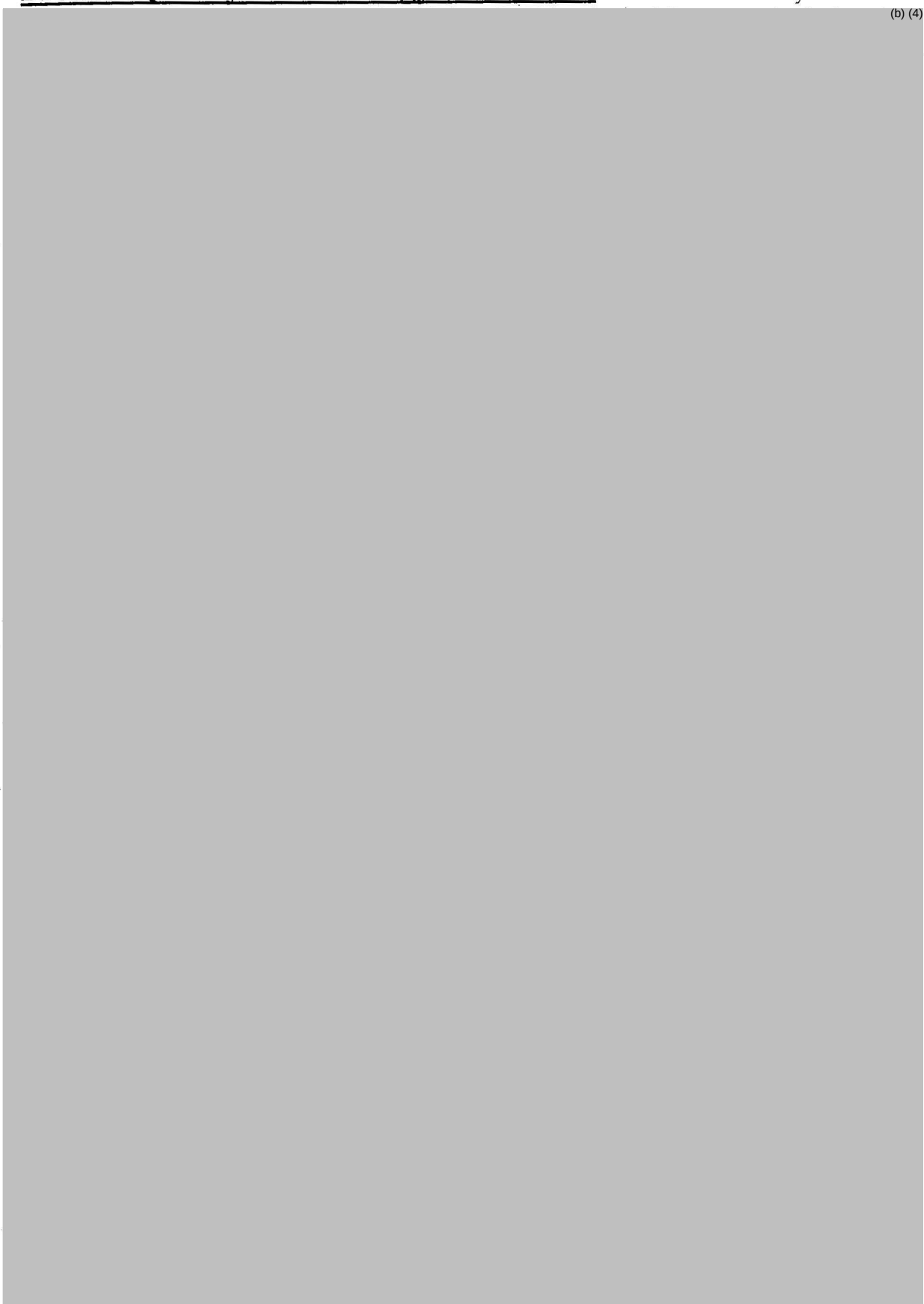
C. CC Block

cc: Original ANDA 76-527
Division File
Field Copy

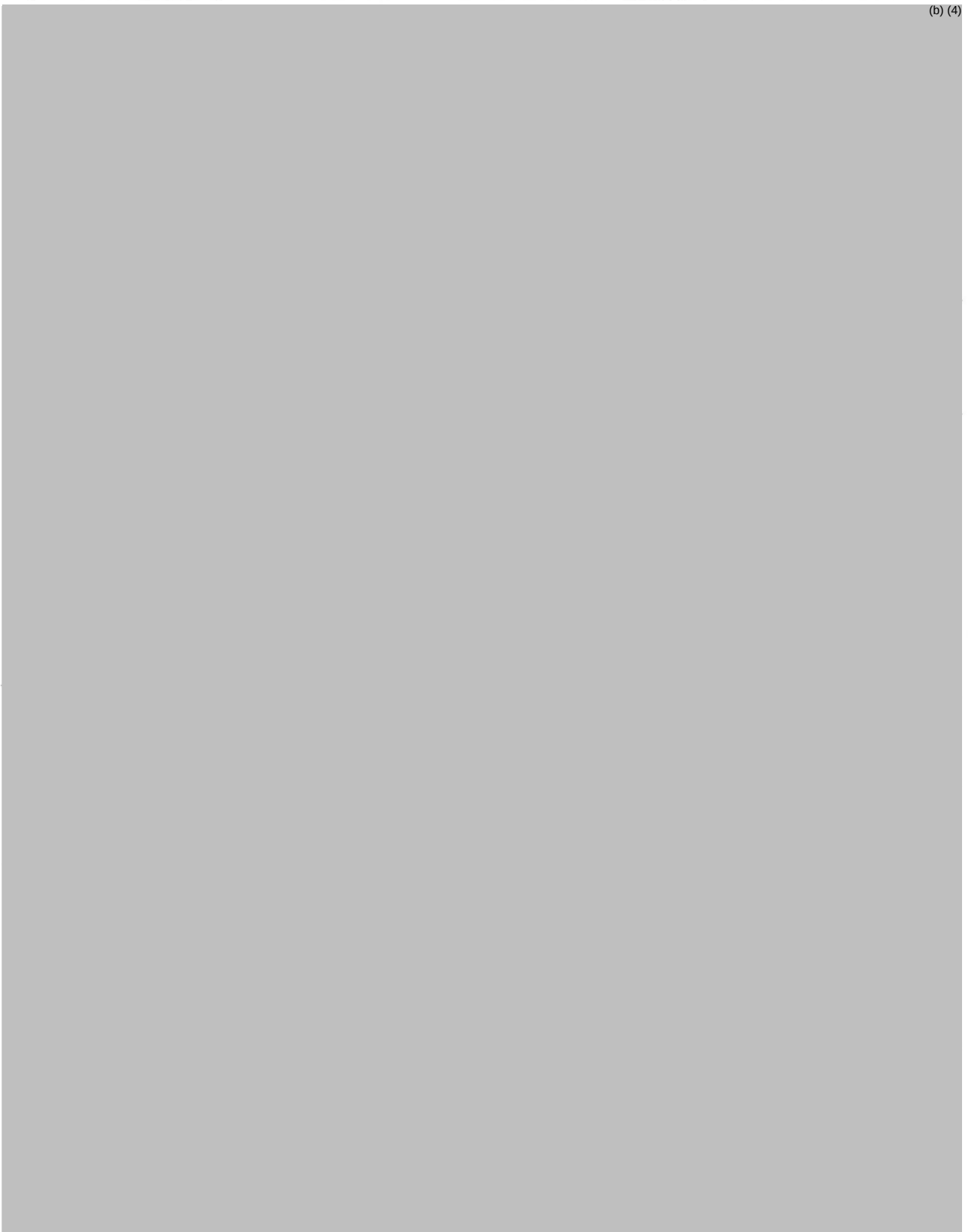
Neal J. Sweeney
10-17-03

Product Quality Microbiology Assessment

(b) (4)



(b) (4)



Product Quality Microbiology Review

Review for HFD-620

August 29, 2003

ANDA: 76-527

Drug Product Name

Proprietary: N/A

Non-proprietary: Ofloxacin Otic Solution 0.3%

Drug Product Classification: N/A

Review Number: #2

Subject of this Review

Submission Date: July 8, 2003

Receipt Date: July 10, 2003

Consult Date: N/A

Date Assigned for Review: July 28, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): October 28, 2002

Date(s) of Previous Micro Review(s): June 2, 2003

Applicant/Sponsor

Name: Novex Pharma

**Address: 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada
L4C 5H2**

U.S. Agent

Name: Apotex Corp.

Address: 616 Heathrow Drive, Lincolnshire, IL 60069

Representative: Marcy MacDonald, Director, Regulatory Affairs

Telephone: 847-279-7740

Name of Reviewer: Lisa S.G. Shelton

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:**
Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile solution/drops, Otic, 0.3%, packaged in 5 mL and 10 mL (b) (4) bottles (b) (4)
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Antibacterial - Quinolones
- B. SUPPORTING/RELATED DOCUMENTS:**
(b) (4)
- C. REMARKS:** None.

filename: V:\MICROREV\76-527a1.doc

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 manufactured under (b) (4)

[REDACTED]

B. Brief Description of Microbiology Deficiencies –

The revalidation program for (b) (4)

[REDACTED]

C. Assessment of Risk Due to Microbiology Deficiencies –

The safety risk associated with the microbiology deficiencies is moderate.

III. Administrative

A. Reviewer's Signature Lisa S.G. Shelton

B. Endorsement Block

Microbiologist, Lisa S.G. Shelton, Ph.D. *8/29/03*

Microbiology Team Leader, Neal J. Sweeney, Ph.D.

C. CC Block

cc: Original ANDA 76-527

Division File

Field Copy

Neal J. Sweeney
8-29-03

Product Quality Microbiology Review

Review for HFD-620

June 2, 2003

ANDA: 76-527

Drug Product Name

Proprietary: N/A

Non-proprietary: Ofloxacin Otic Solution 0.3%

Drug Product Classification: N/A

Review Number: #1

Subject of this Review

Submission Date: October 28, 2002

Receipt Date: November 4, 2002

Consult Date: N/A

Date Assigned for Review: April 9, 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: Novex Pharma

**Address: 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada
L4C 5H2**

U.S. Agent

Name: Apotex Corp.

Address: 616 Heathrow Drive, Lincolnshire, IL 60069

Representative: Marcy MacDonald, Director, Regulatory Affairs

Telephone: 847-279-7740

Name of Reviewer: Lisa S.G. Shelton

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:**
Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile solution/drops, Otic, 0.3%, packaged in 5 mL and 10 mL (b) (4) with (b) (4)
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Antibacterial - Quinolones
- B. **SUPPORTING/RELATED DOCUMENTS:**
(b) (4)
- C. **REMARKS:** Significant parts of the subject review are similar to ANDA 76-513, authored by N. Nath.

filename: V:\MICROREV\76-527.doc

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 manufactured under (b) (4)

[Redacted]

B. Brief Description of Microbiology Deficiencies –

The composition of the drug product (b) (4)

[Redacted]

C. Assessment of Risk Due to Microbiology Deficiencies –

The safety risk associated with the microbiology deficiencies is moderate.

III. Administrative

A. Reviewer's Signature Lisa S.G. Shelton

B. Endorsement Block

Microbiologist, Lisa S.G. Shelton, Ph.D. Yes 6/2/03
Microbiology Team Leader, Neal J. Sweeney, Ph.D.

C. CC Block

cc: Original ANDA 76-527
Division File
Field Copy

Neal J. Sweeney 6/3/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-527

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76.527 Applicant Apotex
 Drug Flonase olic Strength(s) 0.5% Suspension

APPROVAL APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

1. Martin Shimer
 Chief, Reg. Support Branch

DRAFT Package

Date 8 Nov 2005
 Initials MS

FINAL Package

Date 11/18/05
 Initials Paul H

Contains GDEA certification: Yes No Determ. of Involvement? Yes No
 (required if sub after 6/1/92)

Patent/Exclusivity Certification: Yes No Pediatric Exclusivity System
 If Para. IV Certification- did applicant RLD = NDA # 20-199

Notify patent holder/NDA holder Yes No Date Checked 11/18/05
 Was applicant sued w/in 45 days: Yes No Nothing Submitted

Has case been settled: Yes No Written request issued

Is applicant eligible for 180 day Study Submitted

Generic Drugs Exclusivity for each strength: Yes No Date settled:

Date of latest Labeling Review/Approval Summary 7/28/2005

Any filing status changes requiring addition Labeling Review Yes No

Type of Letter: PT to 1741 - 30 months has expired

Comments: Apotex eligible for 180 Day Exclusivity

2. Project Manager, Team 3
 Review Support Branch

Date _____ Date _____
 Initials _____ Initials _____

Original Rec'd date 10/24/02 EER Status Pending Acceptable OAI

Date Acceptable for Filing 11/4/02 ✓ Date of EER Status 11/2/05

Patent Certification (type) 15 Date of Office Bio Review 3/25/03

Date Patent/Exclus. expires 3/27/2012 Date of Labeling Approv. Sum 7/28/05

Citizens' Petition/Legal Case Yes No Labeling Acceptable Email Rec'd Yes No

(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes No

First Generic Yes No Date of Sterility Assur. App. 10/12/03

Methods Val. Samples Pending Yes No

MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date _____

Previously reviewed and CGMP def. /NA Minor issued Date _____

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included ✓

OGD Regulatory Counsel, Post-MMA Language Included

Comments: see REV 3.1 version.

Date 11/9/05

Initials DR

4. Div. Dir./Deputy Dir.
 Chemistry Div. I II OR III

Comments:

Date 11/10/05

Initials PS

CAC OTI

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only
 Assoc. Dir. For Chemistry
 Comments: (First generic drug review)

Date _____
 Initials _____

N/A. ANDAs for this drug product have been tentatively approved for Bausch + Lomb (76-128) and Hi-Tech (76-616).

6. Vacant
 Deputy Dir., DLPS

Solution
 RLD = Flox in Otis Drops 0.3%
 Daiichi Pharmaceutical Company Ltd.
 NDA 20-799 (001)

Date _____
 Initials _____

7. Peter Rickman
 Director, DLPS

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No

Date 11/18/05
 Initials Paul for

Comments: Acceptable LRS dated 11/2/05 (Verified 11/18/05). No OAT Alerts noted. Bioequivalence waiver granted under 21 CFR 320.22 (b)(1) Office-level bioequivalence 3/25/03. Microbiology/sterility assurance found acceptable 10/17/03. FPI found acceptable 11/4/05. (b)(4) approval 1/18/05 as found acceptable via OGD information package. CMC found acceptable for approval 11/18/05. Methods validation was completed & found acceptable.

8. Robert L. West
 Deputy Director, OGD

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No

Date 11/18/2005
 Initials Robert West

Comments: Apotex made a paragraph 4 certification to the '741 patent. Apotex was sued within the 45-day period. The 30-month statutory period for this litigation expired on 8/6/05.

This ANDA is recommended for approval. Apotex is eligible for 180-day generic drug exclusivity for this drug product.

9. Gary Buehler
 Director, OGD

Comments:

Date 11/18/05
 Initials Paul for

First Generic Approval

PD or Clinical for BE

Special Scientific or Reg. Issue

10. Project Manager, Team
 Review Support Branch

Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

Time notified of approval by phone 1:20 PM Time approval letter faxed

FDA Notification:

Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORIG AMENDMENT

N/AM

October 17, 2005

Ms. Ann Vu
Project Manager
Office of Generic Drugs - HFD-600
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Vu:

Re: RESPONSE TO TELEPHONE AMENDMENT
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

Further to your telephone conversation with Robin Windover on October 13, 2005 regarding the review of our Abbreviated New Drug Application, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review we have prepared our response in a question-and-answer format. An Application Form FDA 356h has been included as Attachment No. 1 and a signed Field Copy Certification has been included as Attachment No. 2.

1. *Please provide shelf-life stability data to support your proposed (b) (4) expiry date.*

Response: As requested, (b) (4) shelf-life stability data for batches 1X630 and 1X640 has been provided in Attachment No. 3.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

RECEIVED

OCT 18 2005

OGD/CDER

October 13, 2005

ORIG AMENDMENT

N/AM

Ms. Ann Vu
Project Manager
Office of Generic Drugs - HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Vu:

Re: RESPONSE TO TELEPHONE AMENDMENT
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

Further to the telephone message that you left with Robin Windover on October 11, 2005 regarding the Chemistry Minor Amendment submitted on August 11, 2005, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review we have prepared our response in a question-and-answer format. An Application Form FDA 356h has been included as Attachment No. 1 and a signed Field Copy Certification has been included as Attachment No. 2.

1. Please amend the degradation product limits in your table to reflect the ICH limits as follows: Identification Threshold is NMT ^{(b) (4)}% and Qualification Threshold is NMT ^{(b) (4)}%

Response: As requested, the table has been amended and included below:

Degradation Products	Current Specification	Limit as per MDD and ICH
Known ^{(b) (4)}	Finished Product Stability NMT ^{(b) (4)} % NMT ^{(b) (4)} %	NMT ^{(b) (4)} %
Individual Unknown	Finished Product & Stability NMT ^{(b) (4)} %	NMT ^{(b) (4)} %
Total	Finished Product Stability NMT ^{(b) (4)} % NMT ^{(b) (4)} %	N/A

RECEIVED

OCT 14 2005

OGD / CDER

.../cont'd

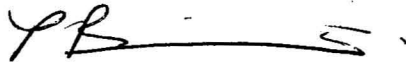
APOTEX INC.
RESPONSE TO
TELEPHONE AMENDMENT

Ofloxacin Otic Solution, 0.3%
ANDA No. 76-527
October 13, 2005

- 2 -

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'PB', followed by a horizontal line and a small flourish.

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

August 11, 2005

ORIG AMENDMENT

N/AM

Ms. Ann Vu
Project Manager
Office of Generic Drugs - HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Vu:

Re: CHEMISTRY MINOR AMENDMENT
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

Further to the telephone conversation between you and Robin Windover (Apotex Inc.) on August 02, 2005, we are pleased to provide you with our Chemistry Minor Amendment in triplicate (Archival, Review and Field copies). This Chemistry Minor Amendment is to notify FDA that we responded to our last microbiology deficiency on September 16, 2003 and to request FDA to perform a final review of the chemistry portion of our ANDA application based on ICH requirements. An Application Form FDA 356h for this amendment has been prepared and is enclosed as Attachment No. 1. In addition, a Field Copy Certification is provided in Attachment No. 2.

We have evaluated our drug substance, reference standard, finished product and stability specifications against current ICH requirements. The drug substance and reference standard specifications have been revised to comply with ICH requirements. The drug product and stability specifications were found to meet all ICH requirements and therefore we believe the specifications do not require any further changes at this time. A comparison table and explanation of the changes has been provided in Attachment No. 3. Copies of the proposed drug substance and reference standard specifications have been included in Attachment No. 4.

In addition, further to the Minor Amendment that was received on December 08, 2003 regarding the method validation results we would like to take the opportunity to close out the file on this amendment. As per the telephone conversation between you and Gina Sirianni (Apotex Inc.) on October 26, 2004 the district lab performed a retest on our product and they had no further difficulties with our method.

RECEIVED

.../cont'd

AUG 12 2005

OGD/CDER



Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,



cc: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

August 08, 2005

Ms. Beverly Weitzman
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

HAT
P 11/2/05
MC

Dear Ms. Weitzman,

**Re: CONTROLLED CORRESPONDENCE – Labeling Decision for
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527**

This letter is to inform you that we have received notification from our legal council that the agency has made a decision to accept our request to [REDACTED] (b) (4)

[REDACTED] Cecelia Parise of OGD's Regulatory Support Group conveyed the details of the decision to our legal council on August 05, 2005. In light of this information, we would like to request that you complete your review of the gratuitous labeling amendment that was submitted on June 02, 2004 and advise us as soon as possible if any further changes are required. A signed Application Form FDA 356h has been prepared and included for review.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,



for Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

cc: Peter Rickman, Director, Division of Labeling and Program Support, OGD
William A. Rakoczy, Council for Apotex Inc.
Robert Breisblatt, Council for Apotex Inc.
Julie Katz, Council for Apotex Inc.

RECEIVED

AUG 10 2005

OGD/CDER





NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050

Facsimile 905 884-9876

ORIGINAL

June 10, 2004

XS

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Mr. Buehler:

Re: Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

There has been some restructuring within the Apotex Group of Companies to formally reflect that they are part of Apotex Inc. Effective immediately, the names of the various sites that make up the Apotex Group have changed.

Novex Pharma (a Division of Apotex Inc.) will now be named Apotex Inc. and will be distinguished from other locations by referring to it as the Richmond Hill Site.

A signed Application Form FDA 356h has been provided with this letter for the above-mentioned product. A complete listing of Novex Pharma's approved ANDAs and ANDAs currently under review by the Agency has been appended to this letter.

If you have any questions, please do not hesitate to contact me by phone at (905) 508-2396, by Fax at (905) 884-0357 or email at pbonnici@apotex.com.

Sincerely,
APOTEX INC. - Richmond Hill Site

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:cd

Encl.

RECEIVED
JUN 14 2004
OGD / CDER



NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

2.1
ORIGINAL

Telephone 905 884-2050
Facsimile 905 884-9876

June 02, 2004

Office of Generic Drugs, HFD-600
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

FPL

Dear Sir/Madam:

Re: GRATUITOUS LABELING AMENDMENT
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Labeling Amendment to our unapproved application for Ofloxacin Otic Solution, 0.3%. This Gratuitous Labeling Amendment has been provided in duplicate (Archival and Review copies). A signed Application Form FDA 356h has been prepared and can be found as Attachment No. 1.

This Gratuitous Labeling Amendment is submitted as a result of the change in Novex Pharma's standard labeling format and text, and to update the package insert following a revision to the Reference Listed Drug labelling. In addition, as per our fax transmission to Martin Shimer on January 26, 2004 and subsequent acknowledgement from Beverly Weitzman on February 25, 2004 the package insert has been updated to (b) (4)

In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of Novex Pharma's final printed bottle and carton label, provided in this Amendment and those provided in our Labeling Amendment submitted on July 24, 2003 has been provided in Attachment Nos. 2 and 3, respectively. A side-by-side comparison of Novex Pharma's final printed package insert (prescribing information and patient information), provided in this Amendment and the updated Reference Listed Drug package insert has been provided in Attachment No. 4.

RECEIVED

JUN 03 2004

OGD / CDER

...cont'd

NOVEX PHARMA
GRATUITOUS LABELING
AMENDMENT

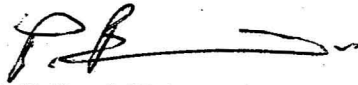
Ofloxacin Otic Solution,
0.3% ANDA No. 76-527
June 02, 2004

- 2 -

Twelve (12) printers proofs of the labeling for the bottle, carton and package insert (prescribing information and patient information) have been provided in Attachment No. 5. We trust that this will be acceptable for final review of our labeling for this product and hereby confirm that the printer's proofs provided are a true representation of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, Novex Pharma will notify the agency, as necessary.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or FAX your requests to (905) 884-0357.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB: rw

Encl.



NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

September 16, 2003

ORIG AMENDMENT

N/AM

Thuyanh Vu
Project Manager
Office of Generic Drugs, CDER, FDA, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Vu:

Re: RESPONSE TO MICROBIOLOGY DEFICIENCIES
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

Further to your Microbiology Deficiencies letter faxed on August 29, 2003, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field copy certification has been included as Attachment No. 3.

A. Microbiology Deficiencies

1.



(b) (4)

RECEIVED

SEP 17 2003

CDER

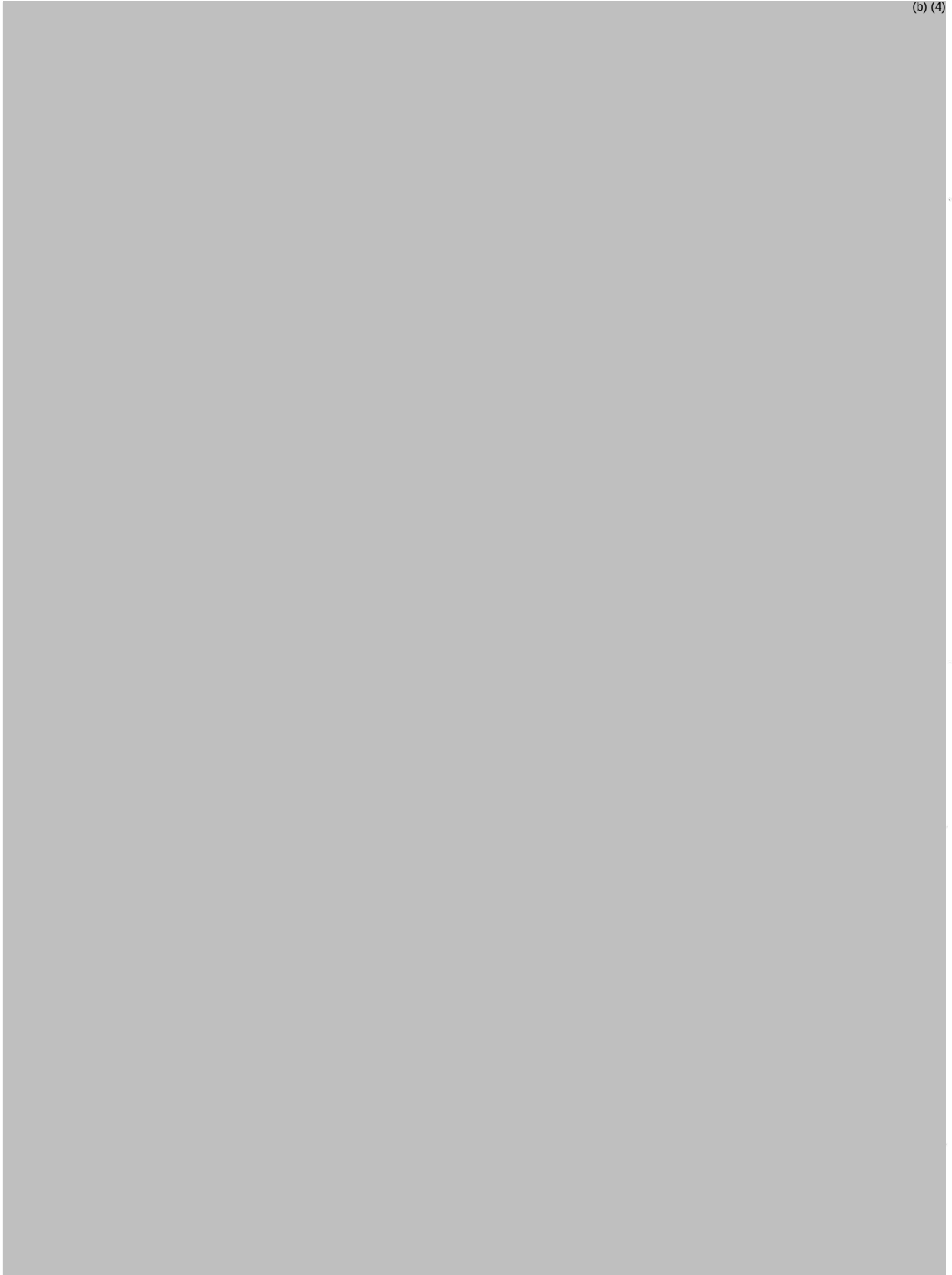
.../cont'd



NOVEX PHARMA
RESPONSE TO MICROBIOLOGY
DEFICIENCIES

Ofloxacin Otic Solution, 0.3%
ANDA No. 76-527
September 16, 2003

- 2 -



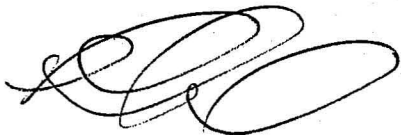
(b) (4)

.../cont'd

(b) (4)

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2445, or FAX your requests to (905) 884-0357.

Yours sincerely,



Gina Sirianni, M.Sc.
Manager, US Regulatory Affairs

GS:mt

Encl.



616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

July 25, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N/AF

FPL

LABELING AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma in Canada, is hereby forwarding in duplicate a label amendment as a result of the change in the standard labeling format.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 847-279-7740

RECEIVED

JUL 29 2003

OGD/CDER



616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

July 8, 2003

ORIG AMENDMENT

N/A

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MICROBIOLOGY AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma in Canada, is forwarding in duplicate a microbiology amendment in response to the FDA microbiology deficiency letter dated June 04, 2003. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 847-279-7740

RECEIVED
JUL 10 2003
OGD/CDER



616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 5, 2003

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

PATENT AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527
Patent No.: 5,401,741

NEW CORRESP

NC

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma in Canada, is forwarding in duplicate a patent amendment regarding the above referenced product.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

A handwritten signature in black ink, appearing to read 'Marcy Macdonald', is written over a large, stylized circular flourish.

Marcy Macdonald
Director Regulatory Affairs
Ext. 223

RECEIVED

MAY 8 - 2003

OGD / CDER

9/2/03
NAT
0/2/03
30 mo ~ 8/1/08

NAT
w
7/9/03

A handwritten signature in black ink, consisting of a stylized 'M' followed by a flourish.



50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 14, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527

ORIG AMENDMENT

N/A

FPL

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Canada, is hereby submitting in duplicate a label amendment in response to the FDA deficiency letter dated March 13, 2003.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED

APR 16 2003

OGD / CDER



50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 27, 2003

ORIG AMENDMENT
N/AM

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Canada, is hereby submitting in duplicate a minor amendment in response to the FDA minor deficiency letter dated January 23, 2003. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
MAR 03 2003
OGD / CDER



NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

February 26, 2003

Thuyanh Vu
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Vu:

Re: MINOR AMENDMENT
Ofloxacin Otic Solution, 0.3%, ANDA No. 76-527

Further to your Minor Amendment letter dated January 23, 2003, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field copy certification has been included as Attachment No. 3.

A. Deficiencies

(b) (4)



.../cont'd

NOVEX PHARMA

MINOR AMENDMENT

ANDA No. 76-527

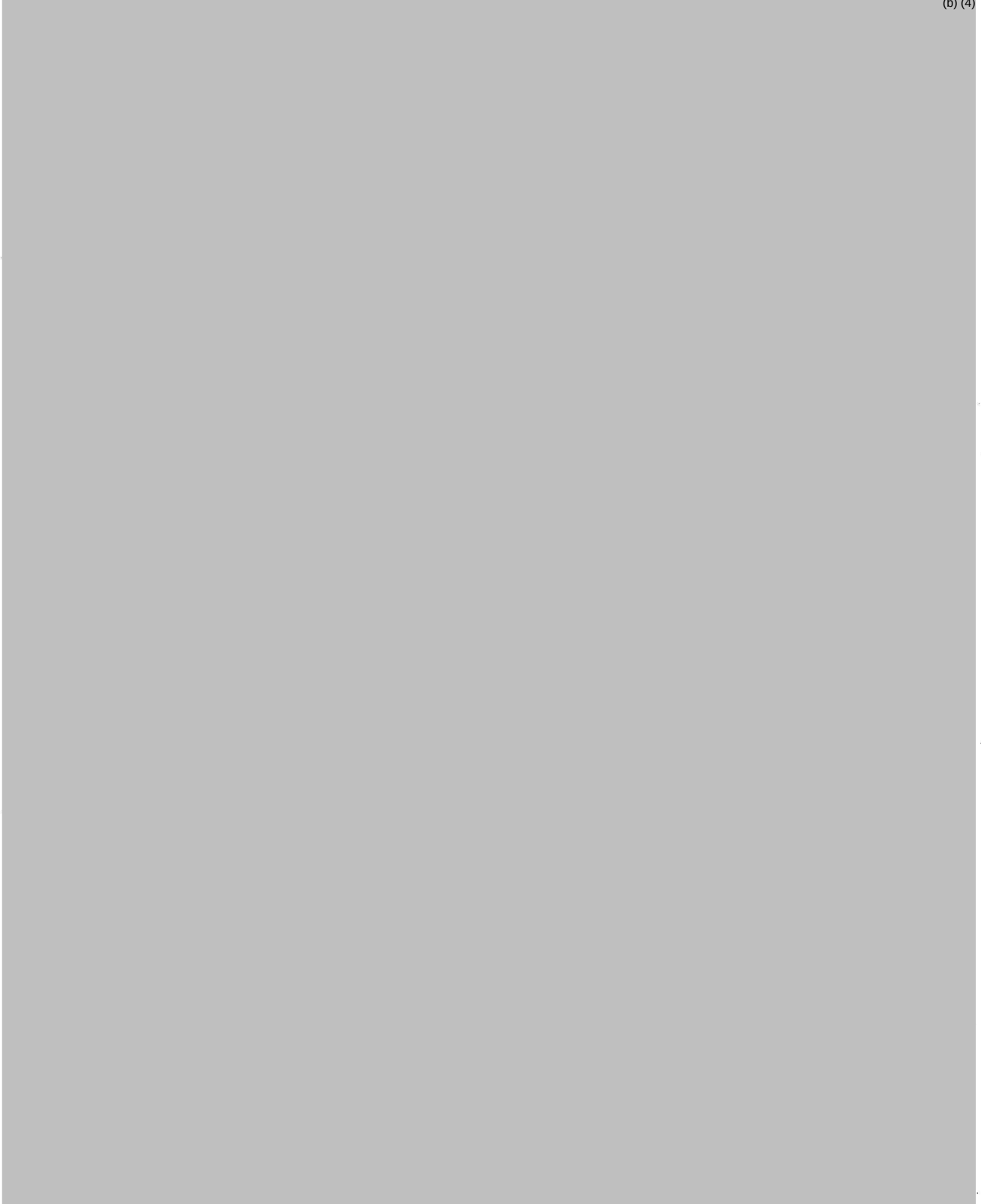
Ofloxacin Otic

Solution, 0.3%,

February 26, 2003

- 2 -

(b) (4)



.../cont'd

NOVEX PHARMA

MINOR AMENDMENT

ANDA No. 76-527

- 3 -

Ofloxacin Otic
Solution, 0.3%,
February 26, 2003

(b) (4)

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,



Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:cd

Encl.



*Etthomas
NPI
3/2/03*

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 25, 2003

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

NEW CORRESP

NC

PATENT AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527
Patent No. 5,401,741

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma in Canada, is submitting proof of patent notifications to the patent holders.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director Regulatory Affairs
Ext. 223

RECEIVED

MAR 03 2003

OGD / CDER

7/1/03



50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 4, 2003

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

NEW CORRESP

PATENT AMENDMENT

RE: Ofloxacin Otic Solution
0.3%
ANDA No. 76-527
Patent No. 5,401,741

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma in Canada, is hereby forwarding a patent amendment in duplicate regarding the above referenced product and patent.

Please note a copy of the return receipts will be provided, as required by 21 CFR 314.95(e) when we receive them back.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
FEB 10 2003
OGD / CDER

Apotex Corp.
U.S. Agent for Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061
|||

Dear Madam:

Reference is made to the telephone conversation dated December 6, 2002 and your correspondence dated December 10, 2002.

DATE OF APPLICATION: October 28, 2002

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

- 1) Each owner of the patent or the representative designated by the owner to receive the notice.
- 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
- 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement, or a settlement agreement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at. (301)827-5862.

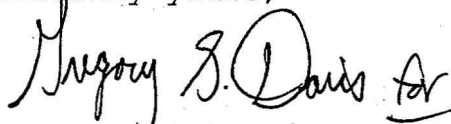
We will correspond with you further after we have had the opportunity to review the application.

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,

A handwritten signature in dark ink, appearing to read "Gregory J. Davis" followed by a stylized flourish or initial.

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

ANDA 76-527

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

HFD-615/ETHomas, CSO

Word File V:\Firmsnz\novex\ltrs&rev\76527.ack

FT/EST 12/16/02

ANDA Acknowledgment Letter!

[Signature] 16-Dec-2002

date

[Signature]

date



50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

December 10, 2002

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

ARCHIVE LETTER

RE: ANDA 76-527
Ofloxacin Otic Solution
0.3%

To Whom It May Concern:

As requested December 6, 2002 by Emily Thomas, OGD, Regulatory Support, Apotex Corp., as the U.S. agent for Novex Pharma, is providing a copy of the Blank Master Packaging Orders for Ofloxacin Otic Solution, 0.3% (5 mL and 10 mL).

Please direct any inquiries regarding this submission to me at the addresses listed above.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

Cc: Emily Thomas, OGD, Regulatory Support

RECEIVED

DEC 12 2002

OGD / CDER

76-527



50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

October 28, 2002

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j)(2)(A) OK
16 DEC 2002
Jugony J. Davis

RE: Ofloxacin Otic Solution USP
0.3%
Original Abbreviated New Drug Application

To Whom It May Concern:

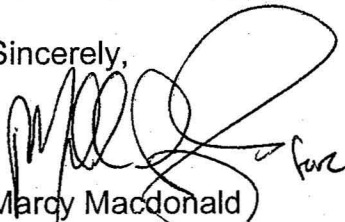
Not USP

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Corp., as the U.S. agent for Novex Pharma of Ontario, Canada, is hereby forwarding an original abbreviated new drug application (ANDA) for Ofloxacin Otic Solution USP, 0.3%.

Enclosed is an archival copy under blue cover, a chemistry review copy under red cover, and the bioavailability/bioequivalence review section under orange cover and a field copy under a burgundy cover.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the addresses listed above.

Sincerely,


Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
NOV 04 2002
OGD / CDER