

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-921 / S-008

Trade Name: Ocuflax®

Generic Name: (ofloxacin ophthalmic solution)

Sponsor: Allergan, Inc

Approval Date: November 9, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-921 / S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-921 / S-008

APPROVAL LETTER

NDA 19-921/S-008

Allergan, Inc.
Attention: Elizabeth Bancroft
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Ms. Bancroft:

Please refer to your supplemental new drug application dated August 25, 1999, received August 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OCUFLOX® (ofloxacin ophthalmic solution) 0.3%.

This supplemental new drug application provides for revised draft labeling of the package insert to add a Geriatric Use subsection to the Precautions section and for additional adverse experiences.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling dated August 25, 1999.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-921/S-008." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-921 / S-008

APPROVED LABELING

OCUFLOX® (ofloxacin ophthalmic solution) 0.3% sterile

DESCRIPTION

OCUFLOX® (ofloxacin ophthalmic solution) 0.3% is a sterile ophthalmic solution. It is a fluorinated carboxyquinolone anti-infective for topical ophthalmic use.

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.

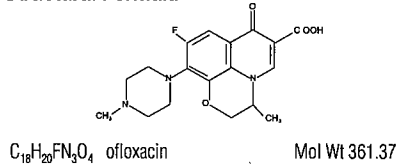
Contents: Active: ofloxacin 0.3% (3 mg/mL);

Preservative: benzalkonium chloride (0.005%);

Inactives: sodium chloride and purified water. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

OCUFLOX® solution is unbuffered and formulated with a pH of 6.4 (range - 6.0 to 6.8). It has an osmolality of 300 mOsm/kg. Ofloxacin is a fluorinated 4-quinolone which differs from other fluorinated 4-quinolones in that there is a six member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.

Structural Formula



CLINICAL PHARMACOLOGY

Pharmacokinetics: Serum, urine and tear concentrations of ofloxacin were measured in 30 healthy women at various time points during a ten-day course of treatment with OCUFLOX® solution. The mean serum ofloxacin concentration ranged from 0.4 ng/mL to 1.9 ng/mL. Maximum ofloxacin concentration increased from 1.1 ng/mL on day one to 1.9 ng/mL on day 11 after QID dosing for 10/12 days. Maximum serum ofloxacin concentrations after ten days of topical ophthalmic dosing were more than 1000 times lower than those reported after standard oral doses of ofloxacin. Tear ofloxacin concentrations ranged from 5.7 to 31 µg/g during the 40 minute period following the last dose on day 11. Mean tear concentration measured four hours after topical ophthalmic dosing was 9.2 µg/g. Corneal tissue concentrations of 4.4 µg/mL were observed four hours after beginning topical ocular application of two drops of OCUFLOX® every 30 minutes. Ofloxacin was excreted in the urine primarily unmodified.

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

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

AEROBES, GRAM-POSITIVE:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

AEROBES, GRAM-NEGATIVE:

Enterobacter cloacae
Haemophilus influenzae
Proteus mirabilis
Pseudomonas aeruginosa
*Serratia marcescens**

ANAEROBIC SPECIES:

Propionibacterium acnes

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

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

AEROBES, GRAM-POSITIVE:

Enterococcus faecalis
Listeria monocytogenes
Staphylococcus capitis

Staphylococcus hominus
Staphylococcus simulans
Streptococcus pyogenes

AEROBES, GRAM-NEGATIVE:

Acinetobacter calcoaceticus var. anitratus
Acinetobacter calcoaceticus var. Iwofii
Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Escherichia coli
Haemophilus parainfluenzae
Klebsiella oxytoca

Klebsiella pneumoniae
Moraxella (Branhamella) catarrhalis
Moraxella lacunata
Morganella morganii
Neisseria gonorrhoeae
Pseudomonas acidovorans
Pseudomonas fluorescens
Shigella sonnei

OTHER:

Chlamydia trachomatis

Clinical Studies:

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

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

INDICATIONS AND USAGE

OCUFLOX® solution is indicated for the treatment of infections caused by susceptible strains of the following bacteria in the conditions listed below:

CONJUNCTIVITIS:

Gram-positive bacteria:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

Gram-negative bacteria:

Enterobacter cloacae
Haemophilus influenzae
Proteus mirabilis
Pseudomonas aeruginosa

CORNEAL ULCERS:

Gram-positive bacteria:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

Gram-negative bacteria:

Pseudomonas aeruginosa
*Serratia marcescens**

Anaerobic species:

Propionibacterium acnes

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

CONTRAINDICATIONS

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

WARNINGS

NOT FOR INJECTION.

OCUFLOX® solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

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

PRECAUTIONS

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

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

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

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

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

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

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

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

Nonteratogenic Effects: Additional studies in rats with doses up to 360 mg/kg/day during late gestation showed no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and well-controlled studies in pregnant women. OCUFLOX® solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Pediatric Use: Safety and effectiveness in infants below the age of one year have not been established. Quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after oral administration; however, topical ocular administration of ofloxacin to immature animals has not shown any arthropathy. There is no evidence that the ophthalmic dosage form of ofloxacin has any effect on weight bearing joints.

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

ADVERSE REACTIONS

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

DOSE AND ADMINISTRATION

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

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

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

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

HOW SUPPLIED

OCUFLOX® (ofloxacin ophthalmic solution) 0.3% is supplied sterile in plastic dropper bottles of the following sizes:

1 mL - NDC 11980-779-01
5 mL - NDC 11980-779-05
10 mL - NDC 11980-779-10

Note: Store at 15-25°C (59-77°F)

Rx only

Revised November 2000

Licensed from: Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan and Santen Pharmaceutical Co., Ltd., Osaka, Japan

U. S. PAT. NOS. 4,382,892; 4,551,456

*Registered Trademarks of Allergan, Inc.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-921 / S-008

MEDICAL REVIEW

Clinical Review of NDA 19-921
Labeling Supplement

NDA 19-921/S-008

Submission Date: 8/25/99
Receipt Date: 8/27/99
Review Date: 9/15/99

Applicant: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Applicant's Representative: Elizabeth Bancroft
Director, Regulatory Affairs

Drug: OCUFLOX® (ofloxacin ophthalmic solution) 0.3%

Pharmacologic Category: Anti-bacterial

Submitted: Revised draft labeling to add a Geriatric Use subsection and adverse experiences to the package insert.

Following is the labeling submitted by the company. Reviewer recommended deletions are noted by ~~strikeout~~ and additions by double underline within the review.

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ALLERGAN

OCUFLOX®

(ofloxacin ophthalmic solution) 0.3%

sterile

DESCRIPTION

OCUFLOX® (ofloxacin ophthalmic solution) 0.3% is a sterile ophthalmic solution. It is a fluorinated carboxyquinolone anti-infective for topical ophthalmic use.

Structural formula:

ofloxacin

$C_{18}H_{20}FN_3O_4$

Mol Wt 361.37

Chemical Name:

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

Contains: Active: Ofloxacin 0.3% (3 mg/mL)

Preservative: Benzalkonium chloride (0.005%). **Inactives:** sodium chloride and purified water. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

OCUFLOX® solution is unbuffered and formulated with a pH of 6.4 (range-6.0 to 6.8). It has an osmolality of 300 mOsm/kg. Ofloxacin is a fluorinated 4-quinolone which differs from other fluorinated 4-quinolones in that there is a six member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.

CLINICAL PHARMACOLOGY

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

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

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

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

Cross resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has been shown to be active against most strains of the following organisms both in vitro and, clinically, in conjunctival and/or corneal ulcer infections as described in the **INDICATIONS AND USAGE** section.

AEROBES, GRAM-POSITIVE:	AEROBES, GRAM-NEGATIVE:
<i>Staphylococcus aureus</i>	<i>Enterobacter cloacae</i>
<i>Staphylococcus epidermidis</i>	<i>Haemophilus influenzae</i>
<i>Streptococcus pneumoniae</i>	<i>Proteus mirabilis</i>
ANAEROBIC SPECIES:	<i>Pseudomonas aeruginosa</i>
<i>Propionibacterium acnes</i>	<i>Serratia marcescens*</i>

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

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

AEROBES, GRAM-POSITIVE:	
<i>Enterococcus faecalis</i>	<i>Staphylococcus hominus</i>
<i>Listeria monocytogenes</i>	<i>Staphylococcus simulans</i>
<i>Staphylococcus capitis</i>	<i>Streptococcus pyogenes</i>

AEROBES, GRAM-NEGATIVE:	
<i>Acinetobacter calcoaceticus</i>	<i>Klebsiella pneumoniae</i>
var. <i>anitratus</i>	
<i>Acinetobacter calcoaceticus</i>	<i>Moraxella (Branhamella)</i>
var. <i>Iwoffi</i>	<i>catarrhalis</i>

Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Escherichia coli
Haemophilus parainfluenzae
Klebsiella oxytoca

Moraxella lacunata
Morganella morganii
Neisseria gonorrhoeae
Pseudomonas acidovorans
Pseudomonas fluorescens
Shigella sonnei

OTHER:

Chlamydia trachomatis

Clinical Studies:

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

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

INDICATIONS AND USAGE

OCUFLOX[®] solution is indicated for the treatment of infections caused by susceptible strains of the following bacteria in the conditions listed below:

CONJUNCTIVITIS:

Gram positive bacteria:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

Gram-negative bacteria:

Enterobacter cloacae
Haemophilus influenzae
Proteus mirabilis
Pseudomonas aeruginosa

CORNEAL ULCERS:

Gram-positive bacteria:

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

Gram-negative bacteria:

Pseudomonas aeruginosa
*Serratia marcescens**

Anaerobic species:

Propionibacterium acnes

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

CONTRAINDICATIONS

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

WARNINGS

NOT FOR INJECTION.

OCUFLOX® solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

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

PRECAUTIONS

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

The systemic administration of quinolones, including ofloxacin, has led to lesions or erosions of

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

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

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

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

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

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

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

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

Nonteratogenic Effects. Additional studies in rats with doses up to 360 mg/kg/day during late

gestation showed no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn.

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

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

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

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

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

Reviewer's comments: *The Geriatric Use subsection has been added. The proposed wording is acceptable.*

ADVERSE REACTIONS

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

Reviewer's comments: *Ocular edema and nausea were added. Acceptable.*

DOSAGE AND ADMINISTRATION

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

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

Days 3 through 7 Instill one to two drops four times daily.

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

Days 1 and 2 Instill one to two drops instilled to the affected eye every 30 minutes, while awake.

Awaken at approximately four and six hours after retiring and instill one to two drops.

Days 3 through 7 to 9 Instill one to two drops hourly, while awake.

Days 7 to 9 through treatment completion Instill one to two drops, four times daily.

HOW SUPPLIED

OCUFLOX® (ofloxacin ophthalmic solution) 0.3% is supplied sterile in plastic dropper bottles of the following size:

1 mL-NDC 11980-779-01

5 mL-NDC 11980-779-05

10 mL-NDC 11980-779-10

Note: Store at 15-25 °C (59-77 °F)

Rx only.

Reviewer's comments: *The statement: "Caution: Federal (U.S.A.) law..." has been replaced with "Rx only." Acceptable.*

August 1999

Allergan America, Hormigueros, Puerto Rico 00660

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labeling may be issued.

Joanne M. Holmes

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cc:

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