PRODUCT MONOGRAPH

PrOCUFLOX®

(ofloxacin)

Ophthalmic Solution 0.3% w/v

Antibacterial Agent

Allergan Inc.
Markham, Ontario
L6G 0B5

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November 24, 1994

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February 6, 2018

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ACTION AND CLINICAL PHARMACOLOGY

The primary mechanism of action of ofloxacin appears to be the specific inhibition of DNA gyrase (topoisomerase II). This enzyme is responsible for the negative supercoiling of bacterial DNA and consequently for its topological configuration, governing functions such as RNA transcription, protein synthesis, DNA replication and repair functions.

INDICATIONS AND CLINICAL USES

OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v is indicated for the treatment of conjunctivitis when caused by susceptible strains of the following bacteria:

Gram Positive Bacteria
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Gram Negative Bacteria
Haemophilus influenza

To reduce the development of drug-resistant bacteria and maintain the effectiveness of OCUFLOX® and other antibacterial drugs, OCUFLOX® should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

CONTRAINDICATIONS

OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v is contraindicated in patients with a history of hypersensitivity to ofloxacin or to any of the components of this medication. A history of hypersensitivity to other quinolones also contraindicates use of ofloxacin.

WARNINGS

OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v is not for injection into the eye.

In patients receiving systemic quinolone therapy, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. Some reactions were

accompanied by cardiovascular collapse, loss of consciousness, tingling, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dypsnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should be administered as clinically indicated.

Stevens-Johnson syndrome has been reported in patients receiving topical ophthalmic ofloxacin; however, a causal relationship has not been established.

Hypersensitivity reactions including angioedema, dyspnea, anaphylactic reaction/shock, oropharyngeal swelling, and tongue swollen have been reported with OCUFLOX® (see Post-Market Adverse Drug Reactions, Immune System Disorders). If an allergic reaction to ofloxacin occurs, discontinue the drug. Use OCUFLOX® with caution in patients who have exhibited sensitivities to other quinolone antibacterial agents.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing OCUFLOX® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of resistant organisms.

Potential for Microbial Overgrowth

Prolonged use of OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v may result in overgrowth of nonsusceptible organisms, including fungi. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. If the infection is not improved within 7 days, cultures should be obtained to guide further treatment. If such infections occur, discontinue use and institute alternative therapy.

PRECAUTIONS

General: The systemic administration of quinolones 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 150 times the maximum recommended daily adult ophthalmic dose), has been associated with these types of effects.

Corneal precipitates, and corneal perforation in patients with pre-existing corneal epithelial defect/corneal ulcer, have been reported during treatment with topical ophthalmic ofloxacin. However, a causal relationship has not been established.

The preservative in OCUFLOX®, benzalkonium chloride, may be absorbed by and cause discoloration of soft contact lenses. OCUFLOX® should not be administered while wearing soft contact lenses.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

Pregnancy: There have been no adequate and well-controlled studies performed in pregnant women. Since systemic quinolones have been shown to cause arthropathy in immature animals, OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because ofloxacin taken systemically is excreted in breast milk, and there is potential for harm to nursing infants, a decision should be made whether to temporarily discontinue nursing during therapy or not to administer the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v in children have not been established.

Geriatric Use: No comparative data are available with topical ofloxacin therapy in this age category versus other age groups.

Drug Interactions: Specific drug interaction studies have not been conducted with OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v. Interactions between ofloxacin and caffeine have not been detected. Systemic use of ofloxacin with non-steroidal anti-inflammatory drugs has shown that the risk of CNS stimulation and convulsive seizures may increase. A pharmacokinetic study in 15 healthy males has shown that the steady-state peak theophylline concentration increased by an average of approximately 9% and the AUC increased by an average of approximately 13% when oral ofloxacin and theophylline were administered concurrently.

ADVERSE REACTIONS

General
Since a small amount of ofloxacin is systemically absorbed after topical administration, adverse events reported with systemic use could possibly occur.

Ophthalmic Use of Ofloxacin:
The most frequently reported drug-related adverse reaction was transient ocular burning or discomfort. Other reported reactions were ocular irritation, redness, stinging, itching, photophobia, tearing and dryness. One report of dizziness, one report of headache and one spontaneous report of toxic epidermal necrolyis have also been received.

Systemic Effects of Ofloxacin:
As with all topical ophthalmic drugs, the potential exists for systemic effects. Ofloxacin used systemically has rarely been associated with serious side effects. Serious reactions reported for systemic dosing of ofloxacin include convulsions and increased intracranial pressure. For the oral dosage form of ofloxacin, gastrointestinal symptoms, mainly nausea/vomiting, pain/discomfort, diarrhea and anorexia, were reported most frequently, followed by central nervous system events (such as dizziness and headaches) and dermatological or hypersensitivity reactions. Additional effects seen with systemic dosing of ofloxacin and other fluoroquinolones are QT prolongation, exacerbation of myasthenia gravis symptoms, tendinitis and tendon rupture. Photophobia was reported rarely in clinical trials with systemic ofloxacin and phototoxicity has been reported with other drugs in this class.

Post-Market Adverse Drug Reactions:

The following adverse reactions have been identified during postmarketing use of OCUFLOX® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Eye Disorders:

Conjunctivitis, dry eye, eye edema, eye pain, foreign body sensation in eyes, hypersensitivity (including eye pruritus, eyelids pruritus), keratitis, lacrimation increased, ocular hyperemia, photophobia, vision blurred.

Gastrointestinal Disorders:
Nausea

General Disorders and Administrative Site Conditions:
Facial edema

Immune System Disorders:
Hypersensitivity (including angioedema, dyspnea, anaphylactic reaction/shock, oropharyngeal swelling and tongue swollen).

Nervous System Disorders:
Dizziness

Skin and Subcutaneous Tissue Disorders:
Periorbital edema

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of accidental ingestion of 10 mL of OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v, only 30 mg of ofloxacin would be ingested. Although this amount may not be clinically significant in terms of overdosage, there could be an increased potential for systemic reactions.

A topical overdosage of OCUFLOX® ophthalmic solution is considered a remote possibility. Discontinue medication if heavy or protracted use is suspected. In the event of a topical overdose, flush the eye with a topical ocular irrigant.

DOSAGE AND ADMINISTRATION

One to two drops every two to four hours for the first two days, and then four times daily in the affected eye(s) for 8 days.

If superinfection occurs or if clinical improvement is not noted within seven days, discontinue use and institute appropriate therapy.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

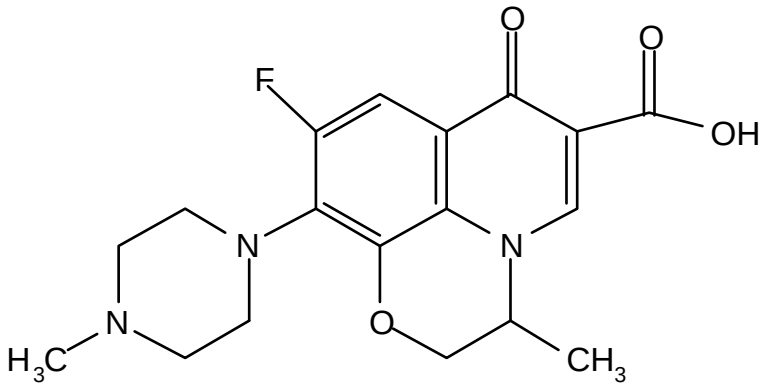
The preservative in OCUFLOX®, benzalkonium chloride, may be absorbed by and cause discoloration of soft contact lenses. OCUFLOX® should not be administered while wearing soft contact lenses.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Common Name:	Ofloxacin (INN, USAN, BAN)
Chemical Name:	(±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-l-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4 benzoxazine-6-carboxylic acid. CAS-82419-36-1

Structural Formula:



Molecular weight:	361.37
Molecular formula:	$C_{18}H_{20}FN_3O_4$
Melting point:	260-270° (with decomposition)
Appearance:	Cream to pale yellow crystalline powder
Solubility:	Soluble in glacial acetic acid, sparingly soluble in chloroform, slightly soluble in water, methanol, ethanol or acetone

COMPOSITION

OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v contains 0.3% w/v ofloxacin with the following non-medicinal ingredients: benzalkonium chloride 0.005% w/v (as preservative); sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water.

STABILITY AND STORAGE RECOMMENDATIONS

OCUFLOX® (ofloxacin) ophthalmic solution 0.3% is sterile in the unopened package, and is stable for 24 months when stored at 15° to 25°C.

AVAILABILITY OF DOSAGE FORMS

OCUFLOX® (ofloxacin) ophthalmic solution 0.3% w/v is available for topical ophthalmic administration as a 0.3% w/v sterile solution, and is supplied in plastic dropper bottles of 5 mL.

MICROBIOLOGY

Ofloxacin has *in vitro* activity against both gram-positive and gram-negative organisms. The primary mechanism of action of ofloxacin appears to be the specific inhibition of DNA gyrase (topoisomerase II). This enzyme is responsible for the negative supercoiling of bacterial DNA and consequently for its topological configuration, governing functions such as RNA transcription, protein synthesis, DNA replication and repair functions.

In a four-site study using a modified tube-dilution procedure, the *in vitro* activity of ofloxacin was evaluated against 419 ocular bacterial isolates of 55 species, in media supplemented with Ca^{++} and Mg^{++}. Table 1 includes MIC values for five major ocular pathogens.

TABLE 1
***IN VITRO* ANTIBACTERIAL ACTIVITY OF OFLOXACIN**
AGAINST FIVE MAJOR OCULAR PATHOGENS
IN STUDIES CONDUCTED IN THE USA

Minimum Inhibitory Concentration Range (µg/mL)

ORGANISMS (Number)	MINIMUM	MAXIMUM	MIC_{90}
Staphylococcus aureus (79)*	0.125	4	0.5
Staphylococcus epidermidis (68)	0.125	16	0.5
Pseudomonas aeruginosa (68)	0.25	8	4
Streptococcus pneumoniae (21)	0.125	2	2
Haemophilus influenzae (18)	0.25	4	4

* Number of isolates in parentheses.

***In Vitro* Study of Ocular Isolates from Japanese Clinical Studies:** An *in vitro* evaluation of the activity (MIC) of ofloxacin was conducted using a broth dilution technique, with 2,678 organisms cultured from the infected eyes of subjects enrolled in three clinical trials conducted in the clinics of public hospitals in Japan. The minimum concentrations necessary to inhibit 90% of the strains (MIC_{90})

was 3.13 µg/ml or less for all species tested except various *Pseudomonas species* and for *Streptococcus sanguis* isolates. MIC_{90} values for ocular isolates are listed in Table 2.

TABLE 2
OCULAR ISOLATES FROM JAPANESE CLINICAL STUDIES
Ofloxacin MIC_{90} Values

Bacterial species	**N**	**MIC_{90} (µg/ml)**
Acinetobacter var. anitratum	44	0.39
Acinetobacter var. lwoffii	33	0.39
Alcaligenes denitrificans	10	1.56
Alcaligenes faecalis	24	0.78
Bacillus species	111	0.20
Corynebacterium species	379	3.13
Enterobacter species (3: cloacae, aerogenes and *agglomerans)*	44	0.20
Escherichia coli	8	0.10
Flavobacterium species	22	3.13
Haemophilus aegyptius	59	0.20
Haemophilus influenzae	44	0.20
Klebsiella species (3: oxytoca, pneumoniae and *ozaenae)*	21	0.10
Micrococcus species	73	1.56
Moraxella species	25	0.20
Propionibacterium acnes	66	1.56
Proteus species (5: including mirabilis, vulgaris and *morganii)*	30	0.20
Pseudomonas acidovorans	21	1.56
Pseudomonas aeruginosa	11	1.56
Pseudomonas alcaligenes	32	3.13
Pseudomonas cepacia	75	1.56
Pseudomonas fluorescens	44	0.78
Pseudomonas maltophilia	36	3.13
Pseudomonas paucimobilis	31	0.39
Pseudomonas putida	29	0.78
Pseudomonas species (6: including vescularis and *diminuta)*	16	50.5
Pseudomonas stutzeri	20	0.78
Serratia marcescens	46	0.39
Staphylococcus aureus	335	0.39
Staphylococcus epidermidis	735	0.39
Streptococcus beta-hemolytic	17	1.56
Streptococcus faecalis (Enterococcus faecalis)	14	1.56
Streptococcus pneumoniae	101	3.13
Streptococcus sanguis	96	6.25
Streptococcus species (inc. pyogenes)	35	3.13

Ofloxacin is bactericidal (3 log reduction in 1-2 hours) at 1 to 4 times the MIC.

Susceptibility Testing: Laboratory results from standard single disc susceptibility tests with a 5 µg ofloxacin disc should be interpreted according to the following criteria:

Zone Diameter (mm)	**Interpretation**
≥ 16	Susceptible
13-15	Moderately susceptible
≤ 12	Resistant

Bacterial Resistance: The development of resistance to ofloxacin appears to be related to modification of bacterial DNA gyrase or to permeability changes in the bacterial outer cell membrane. Resistance to ofloxacin *in vitro* usually develops slowly (multiple-step mutation). Plasmid-mediated resistance or enzymatic inactivation have not been reported. Cross resistance among the fluoroquinolones has been observed, but development of clinically significant cross resistance to nonquinolone drugs appears to be uncommon.

PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics: The general pharmacological activities of ofloxacin have been studied in several mammalian species. At the maximum therapeutic dose levels, no effects on the central nervous system, cardiovascular and respiratory system, autonomic response or smooth and skeletal muscle were observed. These results are consistent with the infrequent occurrence of serious adverse effects with systemic clinical use of ofloxacin. Any pharmacological effects observed were frequently associated with doses at least 1000 times the anticipated maximal daily ocular dose.

Systemic Metabolism and Pharmacokinetics: The pharmacokinetics of ofloxacin have been studied in rats, dogs and monkeys. After oral administration, ofloxacin is well absorbed systemically and well distributed to all parts of the body. It is not extensively bound in the sera of the species tested. As with other quinolones, ofloxacin is found concentrated in melanocyte-containing tissues. Its binding to melanin is reversible. The ofloxacin-melanin binding phenomenon did not produce any observable adverse effects in eyes in a 6-month topical study in monkeys and in chronic oral toxicological studies. The drug wash-out from iris/ciliary body and choroid/retina of pigmented rabbits is rapid. Ofloxacin is also detected in the bone cartilage of both immature and adult dogs.

Ofloxacin passes through the placenta and into milk.

The serum elimination half-life of ofloxacin ranges from 5 to 7.5 hours following oral administration. More than 90% of the drug is excreted unchanged in the urine. Ofloxacin does not exert enzyme induction effects on hepatic microsomal enzymes and has little effect on hepatic enzyme inhibition.

Ocular Pharmacokinetics

Animal: After ophthalmic instillation as an eyedrop, ofloxacin is absorbed and distributed to all parts of the eye globe. 0.3% ofloxacin, applied topically to rabbit eyes five times at 5 minute intervals yielded concentrations of 5.6 µg/mL in the bulbar conjunctiva, 5.1 µg/mL in extraocular muscle, 6.5 µg/mL in the cornea, 2.5 µg/mL in the sclera, 1.5 µg/mL in the aqueous humor, 1.0 µg/mL in the iris and ciliary body, 0.05 µg/mL in the vitreous body, a trace in the lens, retina and choroid, and no detectable ofloxacin in the serum one hour after instillation.

Single dose topical administration in rabbit eyes produced average tear concentrations beginning at 2207 µg/g and declining to 34 µg/g 20 minutes post-dosing. The tear concentration was 2.5 µg/g 6 hours post-dosing.

Human: Administering 0.3% ofloxacin topically 4 times daily to the eyes of 30 normal healthy adults resulted in tear ofloxacin concentrations ranging from 1.2 to 22 µg/g (mean 9.2 µg/g) four hours after the first dose on the eleventh day of treatment. The mean tear concentration varied between 5.7 and 31 µg/g during the time period between 5 and 40 minutes after instillation of the second dose on day 11.

In this same study, mean serum plateau levels of 0.97 ng/mL after the first dose (day 1) and 1.66 ng/mL after the 41st dose (day 11) were achieved. The maximum serum level from multiple topical dosing (1.9 ng/mL) was approximately 2000-fold less than the maximum serum level achieved from treatment with a single 300 mg oral dose (4620 ng/mL).

Time to reach 90% of the plateau serum concentration was 0.9 hours after the initial dose on Day 1 compared with 0.5 hours on Day 11, indicating a change in the rate of systemic absorption from ophthalmic dosing. Total drug recovery (urinary excretion of intact drug plus unabsorbed dose recovered from tear overflow) was 78% on day one and 90% on day ten.

Human Pharmacology

Systemic Pharmacokinetics: In systemic pharmacokinetic studies, ofloxacin was rapidly absorbed into the blood stream following oral dosing, with peak serum concentrations (Cmax) increasing in a dose-related manner. There was no significant increase in peak serum ofloxacin concentration following multiple oral administrations. Cumulative urinary recovery of ofloxacin 48 hours after dosing ranged from 83% to 99% of the administered dose. This indicates that ofloxacin is mainly excreted by renal elimination.

Metabolism Characteristics and Metabolites: The metabolism of ofloxacin was studied in five healthy adult male volunteers receiving a single oral dose of a 600 mg mixture of ofloxacin and deuterium-labeled ofloxacin. Ofloxacin and its metabolites were identified, confirmed and quantified using thin layer chromatography, UV spectrophotometry, high pressure liquid chromatography, fluorometry and other methods. Urinary concentration of ofloxacin increased to a maximum of 686.6 µg/ml at 2-4 hours after dosing and was maintained above 273.9 µg/ml 4-24 hours after dosing.

Cumulative urinary excretion of ofloxacin was 79.5% at 48 hours after dosing. Urinary concentrations of desmethyl ofloxacin were 10.4 and 6.6 µg/ml at 2-4 and 12-24 hours after dosing, concentrations of ofloxacin N-oxide were 7.8 and 2.7 µg/ml at 2-4 and 12-24 hours after dosing. Urinary concentrations of these metabolites were less than 2.5% of the excreted concentration of ofloxacin at each time interval.

The results of this study indicate that ofloxacin exists mainly as parent drug *in vivo*, and is excreted mainly unchanged in the urine in humans.

Drug Interactions: Interactions between ofloxacin and caffeine have not been detected. Systemic use of ofloxacin with non-steroidal anti-inflammatory drugs has shown that the risk of CNS stimulation and convulsive seizures may increase. A pharmacokinetic study in 15 healthy males has shown that the steady-state peak theophylline concentration increased by an average of approximately 9% and the AUC increased by an average of approximately 13% when oral ofloxacin and theophylline were administered concurrently.

TOXICOLOGY

Animal Toxicity Studies

Acute Systemic Toxicity: The acute LD_{50} values of ofloxacin were evaluated in several animal species by oral, subcutaneous or intravenous administration. The LD_{50} values for each study are listed in Table 3.

TABLE 3
LD_{50} Values (mg/kg)

----------Route of Administration----------

Species	Sex	Oral	Intravenous	Subcutaneous
Mouse	M	5450	208	>10000
	F	5290	233	>10000
Rat	M	3590	273	7070
	F	3750	276	9000
Dog	M	>200	>70	
	F	>200	>70	
Monkey	M	>500	<1000	
	F	>500	<1000	

Most frequently observed signs in the acute toxicity studies included: vomiting, decreased motor activity, respiratory depression, prostration, convulsions, collapse, and respiratory arrest.

Subacute/Chronic Systemic Toxicity Studies: Ofloxacin was administered in repeated doses in rats, dogs and monkeys for periods of up to 52 weeks. The most notable effect seen in these studies was the effect of ofloxacin on articular cartilage in immature animals. Several special studies of the effects of ofloxacin on articular cartilage were conducted. Orally administered ofloxacin had no effect on articular cartilage in mature rats and dogs. However, in immature animals, daily treatment for 7 days with ofloxacin at 300 mg/kg (but not at 100 mg/kg) in rats and at 10 mg/kg (but not at 5 mg/kg) in dogs produced arthropathic effects.

Studies were conducted to elucidate the mechanism of action, onset, recovery and effects of age and dosage on arthropathy associated with ofloxacin and other quinolones. The studies indicate that toxicity to weight-bearing joints is dose-related at oral dosages far higher than topical ophthalmic dosages and that toxic effects are seen only in growing animals. Damage to joints was partially repairable, although some damage appeared to be permanent. Damage such as erosion of the cartilage occurs in weight-bearing joints where "bubbles" (inconsistencies in growth) have developed in the cartilage.

Other findings from subacute and chronic studies are listed in Table 4.

TABLE 4
SUBACUTE/CHRONIC SYSTEMIC TOXICITY STUDIES

	Species, Strain Age	Initial No. Per Group	Dosages mg/kg/Day	Route	Duration (weeks)	Major Findings
1.	Rat, SD, 6 weeks	10M/10F	0, 30, 90, 270, 810	p.o.	4	No drug related deaths. Enlargement of the cecum in all treatment groups. Slight local rarefaction of surface matrix in articular cartilage of 2 males at 810 mg/kg/day. No drug related alterations in ophthalmoscopy, audiometry, ECG or hematology at any dosage level
2.	Rat, SD 5 weeks	15M/15F	0, 10, 30, 90, 270	p.o.	26	No drug-related deaths. Animals in the high-dose group (270 mg/kg/day) exhibited an increase in water intake, decrease in food intake, increase in salivation, soft stools, urinary staining, increased alkaline phosphatase and SGOT activity, decreased urinary sodium excretion, increased positive fecal occult blood reaction, and a slightly increased amount of lipid droplets in cortical cells of the adrenals. Enlargement of the cecum was observed in 30, 90, and 270 mg/kg/day treatment groups. Enhancement of osteochondrosis-like lesion in the medial femoral condyle was noted in the 90 and 270 mg/kg/day treatment groups.
3.	Dog, beagle, 7 months	3M/3F	0, 12.5, 50, 200	p.o.	4	Cavitation or erosion of the cartilage of distal femur and humerus at 50 or 200 mg/kg/day. No deaths occurred but one male dog receiving 200 mg/kg/day was sacrificed on day 22 in moribund condition. This dog was severely dehydrated and markedly emaciated at necropsy. Bilateral corneal opacities in this animal were the only ophthalmologic changes. Opacities were probably due to dehydration and poor condition changes. Opacities were probably due to dehydration and poor condition

Note: Ofloxacin was administered in a 0.5% carboxymethylcellulose suspension in rats. In dogs and monkeys, it was administered in gelatin capsules.

TABLE 4 (cont'd)
SUBACUTE/CHRONIC SYSTEMIC TOXICITY STUDIES

	Species, Strain Age	Initial No. Per Group	Dosages mg/kg/Day	Route	Duration (weeks)	Major Findings
4.	Monkey, cynomolgus 2-1/2 to 4 years	3M/3F	0, 20, 60, 180	p.o.	4	Two male monkeys in the 180 mg/kg/day group terminated on day 25 following persistent diarrhea. Minimal to mild karyomegaly in liver of one male at 60 mg/kg/day, one male at 180 mg/kg/day (moribund kill) and one female at 180 mg/kg/day. Minimal to mild candidiasis of the esophagus in one male at 20 mg/kg/day and one male at 60 mg/kg/day. Candidiasis more marked in the two monkeys that died prior to the end of the study.
5.	Monkey, cynomolgus (adult)	4M/4F	0, 10, 20, 40	p.o.	52	No deaths. There were no drug-related changes in body weights, food or water consumption, ECG, hematology, and macroscopic or microscopic examinations. There was a low incidence of retinal changes in some treated monkeys, however it is improbable that these changes are treatment-related. There were increases in cholesterol in the 40 mg/kg/day treatment group animals. 40 mg/kg/day was considered a no-effect level.

Note: Ofloxacin was administered in a 0.5% carboxymethylcellulose suspension in rats. In dogs and monkeys, it was administered in gelatin capsules.

Carcinogenic Potential: Because ophthalmic ofloxacin solution is not intended for chronic use, specific carcinogenicity studies were not carried out. Chronic ophthalmic toxicity studies showed no evidence of carcinogenic potential.

Mutagenicity Potential: Predictive tests included: Ames test, REC-Assay, micronucleus test, sister chromatid exchange in cultured Chinese hamster cells and in human peripheral blood lymphocytes, unscheduled DNA repair synthesis test, dominant lethal assay, and *in vitro* and *in vivo* cytogenetic tests.

Extensive tests for mutagenicity showed no mutagenic potential. Mutagenicity tests were conducted with ofloxacin by a number of techniques, both *in vitro* and *in vivo*. Dose-related damage to the DNA of *Bacillus subtilis* was seen in tests using the REC assay technique. The damage to *B. subtilis* DNA is consistent with the mechanism of action of the drug in bacteria and is not predictive of mutagenic potential in eukaryotic cells. No evidence of significant mutagenic effects was seen in other tests in a variety of eukaryotic somatic or germ cells.

Human blood samples were examined after oral dosing with 200 mg/day of ofloxacin for 1 to 10 weeks (equivalent to 50 times the maximum recommended daily ophthalmic dose). No chromosome-damaging effect was seen in the peripherial blood leukocytes.

Fetal Toxicity and Fertility Studies: The effects of ofloxacin on fertility, reproduction and fetal toxicity were studied in rats and rabbits. The studies are summarized in Table 5. No adverse effects on fertility and general reproductive performance were seen in male or female rats from administration of ofloxacin in dosages of 10 mg/kg/day to 360 mg/kg/day, beginning well before mating and continuing through the seventh day of gestation in females.

Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day (equivalent to 13500 times the maximum recommended daily ophthalmic dose) and 160 mg/kg/day (equivalent to 2600 times the daily ophthalmic dose) when administered to pregnant rats and rabbits, respectively. 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. Doses of 810 mg/kg/day and 160 mg/kg/day 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.

TABLE 5
SUMMARY OF OFLOXACIN FERTILITY AND REPRODUCTION STUDIES

	Species, Strain Findings	Initial No. Per Group	Dosages mg/kg/day	Route	Duration of Dosing	Major Findings
1.	Rat	24M/24F	0, 10, 60, 360	p.o.	Males - 63 days prior to mating through Day 7 or Day 21 of female gestation. Females - 14 days prior to mating, during mating period and through Day 7 of gestation.	No adverse effects on fertility or general reproductive performance. Some skeletal variations seen in fetuses, but differences between treated and control groups were not significant.
2.	Rat, SD	36F	0, 10, 90, 810	p.o.	Days 7 through 17 of gestation	No drug related effects at 10 mg/kg/day. At 90 mg/kg/day, decrease in body weight of live fetuses and retardation of degree of ossification. mortality, decrease in body weight gain, retardation of degree of ossification, increased incidence of skeletal variations such as cervical ribs and shortening of 13th rib.
3.	Rabbit, New Zealand White	15F	0, 10, 40, 160	p.o.	Days 6-18 of gestation	No drug related effects observed at 10 or 40 mg/kg/day. Increase in fetal mortality and non-pregnant dams at 160 mg/kg/day. No teratogenic effects.
4.	Rat, SD	7F	810	p.o.	Days of gestation: 7-17, 7-8, 9-10, 11-12, 13-1 4, 15-17	Critical period for development of skeletal variations was 9-10 days. Incidence of shortened 13th ribs and cervical ribs increased in this dosage group and 7-17 day group.

Note: Ofloxacin was administered in a 0.5% carboxymethylcellulose suspension.

TABLE 5 (cont'd)
SUMMARY OF OFLOXACIN FERTILITY AND REPRODUCTION STUDIES

	Species, Strain Findings	Initial No. Per Group	Dosages mg/kg/day	Route	Duration of Dosing	Major Findings
5.	Rat, SD	24F	810, 1100, 1600	p.o.	Days 9-10 of gestation	Body weight of live fetuses in all treated groups significantly lower than control. Retardation of degree of ossification, increased incidence of skeletal variation of the ribs in a dose related fashion
6.	Rat, SD	22F	0, 810	p.o.	Days 9-10 of gestation	Incidence of cervical ribs and shortened 13th ribs increased in fetuses.
7.	Rat, SD	24F	0, 10, 60, 360	p.o.	Day 17 of gestation through Day 20 postpartum	No drug related effects in 10 or 60 mg/kg/day groups. At 360 mg/kg/day, transient decrease in spontaneous motor activity in pups. No other effects on late fetal development, labor, delivery, lactation, neonatal viability or growth.

Note: Ofloxacin was administered in a 0.5% carboxymethylcellulose suspension.

Special Toxicity Studies

Ocular Toxicity: Ocular toxicity studies were conducted in rabbits and monkeys with ofloxacin ophthalmic solutions. Results indicate that ofloxacin ophthalmic solutions are not toxic to the eyes under the conditions tested, including dosing up to 16 times per day. Ocular toxicity studies of up to three months duration are included in Table 6 following this page. Chronic ocular toxicity studies are included in Table 7. No local or systemic toxicity was observed as a result of ocular administration of ofloxacin for up to six months in rabbits or monkeys.

Other Special Toxicity Studies: No evidence of ototoxicity, antigenicity or skin sensitization was seen in guinea pigs. Studies in rabbits revealed no evidence of nephrotoxicity.

Special Studies of Tissue Distribution and Accumulation: Special studies of tissue distribution and accumulation, with special reference to the eye tissues, were conducted due to the tendency of ofloxacin to bind to the pigment melanin, which is present in some ocular structures. Studies with the topical solution showed definite binding to melanin which decreased slowly after withdrawal of the drug. *In vitro* studies with bovine melanin showed the affinity of ofloxacin for melanin to be greater than that of timolol and pilocarpine, but less than that of chloroquine and befunolol. The binding was reversible. A four-week study in pigmented rats revealed no evidence of ocular toxicity after daily oral doses of 100 mg/kg/day. Results of this study were consistent with the lack of ocular toxicity seen in multi-dose ocular and systemic toxicity studies in dogs and monkeys.

Studies conducted specifically to study melanin binding are included in Table 8. Table 9 contains the half-life estimates for ofloxacin in the aqueous humor and lens after oral dosing and the concentrations of ofloxacin found in various ocular tissues after topical dosing.

TABLE 6
OCULAR TOXICITY STUDIES (UP TO THREE MONTHS)

	Species, Strain	Initial No. Per Group	Ocular	Dura-tion	Parameters	Major Findings
a.	Rabbits, New Zealand Albino	6F	1 gtt/16X/day Vehicle (OS) or	7 Days	Condition/behavior	No ocular irritation, discomfort, toxicity or cytotoxicity. No abnormalities in the lens or retina.
		6F	1 gtt/16X/day 0.3% Ofloxacin (OS) and		Ocular damage; Body weight changes; Ocular irritation; Ophthalmoscopy	
		1-2F	Untreated control (OD)			
b.	Rabbits, New Zealand Albino	6F	1 gtt/16X/day 0.5% Ofloxacin (OS) or	7 days	Condition/behavior Ocular irritation Ocular/cornea damage	Neither test solution caused ocular irritation, discomfort, nor cytotoxicity.
		6F 12F	1 gtt/16X/day 1.0% Ofloxacin (OS). and Untreated control (OD)		Ophthalmoscopy Body weight changes	
c.	Rabbits, Albino	2M/2F 3M/3F	Untreated control and 1 gtt/3X/day 0.3% Ofloxacin (OU)	3 Weeks	Transmission electron microscopy and Scanning electron microscopy of the conjunctiva, cornea, angle, iris, lens, ciliary body, retina.	No changes of microstructures were observed in any tissue.

TABLE 6 (cont'd)
OCULAR TOXICITY STUDIES (UP TO THREE MONTHS)

	Species, Strain	Initial No. Per Group	Ocular	Dura-tion	Parameters	Major Findings
d.	Rabbits, Japanese	10M 10M 10M 30M	1 gtt/4X/day Vehicle control (OS) or 1 gtt/4X/day 0.3% Ofloxacin (OS) or 1 gtt/4X/day 0.5% Ofloxacin (OS) and Untreated control (OD)	4 Weeks	Condition/behavior Body weight changes Food consumption Ocular irritation Ocular/corneal damage Funduscopy Urinalysis Hematology Organ weight Histopathology	Neither ocular irritation or corneal epithelial defects were observed. There was no systemic toxicity found in urinalysis, hematology, blood chemistry or histopathology.
e.	Rabbits, New Zealand Albino	15M/15F 15M/15F 15M/15F 45M/45F	1 gtt/4X/day 0.3% Ofloxacin photoirradiated (OS or 1 gtt/4X/day 0.3% Ofloxacin vehicle (OS) or Observed/4X/day Handled only Albino Untreated control (OD)	33 days	Gross ocular observ. Condition/behavior Body weight changes Ophthalmoscopy Hematology Blood chemistry Histopathology Ocular irritation Ocular/cornea damage	Neither test solution caused systemic effects ocular irritation, discomfort, toxicity or cyto toxicity.

TABLE 7
CHRONIC OCULAR TOXICITY STUDIES

	Species, Strain Findings	Initial No. Per Group	Ocular Dosage	Dura-tion	Parameters	Major Findings
1.	Rabbits, New Zealand Albino	20M/20F	1 gtt/4X/day Vehicle control (OS) or	6 mos.	Condition/behavior Ocular irritation Ocular/corneal damage Ophthalmoscopy Body weight changes Hematology Blood chemistry Gross postmortem findings Organ weight Histopathology Ocular/systemic tissue	Neither test solution caused ocular irritation, discomfort, toxicity or cytotoxicity. No systemic treatment or dose related effect on general health, body weight, hematology, serum biochemistry, organ weight or histopathology.
		20M/20F	1 gtt/4X/day 0.3% Ofloxacin (OS) or			
		20M/20F	1 gtt/4X/day 0.5% Ofloxacin (OS) or			
		20M/20F	1 gtt/4X/day 1.0% Ofloxacin (OS) or			
		20M/20F	Observed/4X/day Handled only and			
		100M/100F	Untreated control (OD)			

TABLE 7 (cont'd)
CHRONIC OCULAR TOXICITY STUDIES

	Species, Strain Findings	Initial No. Per Group	Ocular Dosage	Dura-tion	Parameters	Major Findings
2.	Monkeys, Cynomolgus	6M/6F 6M/6F 6M/6F 6M/6F 24M/24F	1 gtt/4X/day Vehicle control (OD) or 1 gtt/4X/day 0.3% Ofloxacin (OD) or 1 gtt/4X/day 0.5% Ofloxacin (OD) or 1 gtt/4X/day 1.0% Ofloxacin (OD) and Untreated control (OS)	6 mos.	Condition/behavior Body weight changes Ophthalmoscopy Hematology Blood chemistry Urinalysis Organ weights Histopathology Slit lamp examinations	No effect on general health, slit lamp, bio-microscopic and ophthalmoscopic exams. No gross ocular and organ histomorphological changes. No treatment related hematology and blood chemistry changes. AST and ALT values elevated in all monkeys including controls at 6 months. Values decreased 5 days later and were not considered due to treatment with ofloxacin.

TABLE 8
MELANIN BINDING

Species, Strain, Age	Initial # Per Group	Test Drug	Dosages, mg/kg/day	Route	Duration of Dosing	Major Findings
a. Rats, Pigmented HOS:ACI/N 6 weeks	5M/5F	Ofloxaci n Cinoxacin Chloroquine 0.5% CMC* (Control)	100 100 80 10ml	p.o.	4 weeks	Ofloxacin is not oculotoxic to pigmented rats. Abnormal respira tory behavior observed sporadically in all test animals.
b Rabbits, pigmented	3	Ofloxacin 0.3% Drop	1gtt/3X/da y	Ocular	2 weeks	Ofloxacin may be bound to melanin-containing tissues such as iris/ciliar y body and retina/choroid at relatively high concentrations, and be retained at low levels up to 9 weeks after multiple administration.
Rabbits, Japanese White albino	3					
c. Bovine ocular melanin		Ofloxacin Chloroquine Befunolol Pilocarpine Maleate Timolol Maleate		In vitro		Melanin affinity of ofloxacin is less than that of chloroquine or befunolol and higher than that of timolol and pilocarpine.. Binding was reversible

*0.5% carboxymethylcellulose also served as the vehicle for the test solutions.

TABLE 9
OFLOXACIN CONCENTRATIONS IN OCULAR TISSUES

Species, Strain	Initial # Per Group	Test Drug	Dosage	Route	Duration of Dosing	Major Findings
a. Dogs, Beagle	3M/3F	Ofloxacin	32 mg/kg/day	p.o.	3 weeks	After 21st daily dose, mean maximum ofloxacin concentrations (C_{max}) were 2.8 μg/ml in aqueous humor and 6.2 μg/ml in lens, and terminal elimination half-lives were ~55 hr in aqueous humor and ~60 hr in lens. No ocular toxicity was observed.
b. Rabbits, pigmented	3	Ofloxacin 0.3% eyedrop	1gtt/3X/da y	Ocular	2 weeks	Mean ocular concentrations in pigmented rabbits 2 hours after the last dose were <0.32 μg/g in nicitating membrane, <0.61 μg/g in conjunctiva, 1.06 μg/g in sclera, 1.67 μg/g in cornea, 0.19 μg/ml in aqueous humor, 5.32 μg/g in iris/ciliary body, <0.05 μg/g in lens, ND* in vitreous humor, and 1.82 μg/g in retina/choroid.
Rabbits, Japanese White	3					Mean ocular concentrations in albino rabbits 2 hours after the last dose were <0.34 μg/g in nicitating membrane, <0.92 μg/g in conjunctiva, 0.44 μg/g in sclera, 2.03 μg/g in cornea, 0.46 μg/ml in aqueous humor, 0.74 μg/g in iris/ciliary body, ND* in lens, ND* in vitreous humor, and <0.33 μg/g in retina/choroid. The re was no great difference between albino and pigmented rabbits, except in iris/ciliary body and retina/choroid, in which pigmen ted rabbits had >5-fold higher ofloxacin concentrations.
c. Rabbits, albino	36F	Ofloxacin	0.12 mg/drop	Ocular	1 drop	Mean ofloxacin C_{max} (t_{max}) was 2.95 μg/g (15 min) in conjunctiva, 1.62 μg/g (1 hr) in sclera, 3.32 μg/g (1 hr) in cornea, 0.71 μg/ml (30 min) in aqueous humor, 0.95 μg/g (1 hr) in iris/ciliary body, and ND* in lens, vitreous humor, retina/choroid or optic nerve.

*ND=Not detected

TABLE 9 (continued)
OFLOXACIN CONCENTRATIONS IN OCULAR TISSUES

Species, Strain	Initial # Per Group	Test Drug	Dosage	Route	Duration of Dosing	Major Findings
c. Rabbits, albino	36F	Ofloxacin	0.12 mg/drop	Ocular	5 drops/ 20 min	Mean C_{max} (t_{max}) after the last dose was 34.98 μg/g (5 min) in conjunctiva, 7.66 μg/g (5 min) in sclera, 7.78 μg/g (5 min) in cornea, 3.56 μg/ml (1 hr) in aqueous humor, 3.12 μg/g (30 min) in iris/ciliary body, 0.80 μg/g (30 min) in vitreous humor, and ND* in lens, retina/choroid or optic nerve.
d. Rabbits, albino	77M	Ofloxacin	~0.12 mg/drop	Ocular	5 drops/ 20 min	Mean ofloxacin concentrations one hour after the last dose were 5.64 μg/g in conjunctiva, 2.55 μg/g in sclera, 6.51 μg/g in cornea, 1.47 μg/ml in aqueous humor, 1.09 μg/g in iris/ciliary body, trace in lens, 0.05 μg/g in vitreous humor, and trace in choroid/retina.

*ND=Not detected

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INFORMATION FOR THE CONSUMER

PrOCUFLOX®

Ofloxacin Ophthalmic Solution 0.3% w/v

This leaflet is part of the "Product Monograph" published when OCUFLOX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OCUFLOX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

OCUFLOX® is a topical treatment for external eye infections such as conjunctivitis.

Antibacterial drugs like OCUFLOX® treat only bacterial infections. They do not treat viral infections. Although you may feel better early in the treatment, OCUFLOX® should be used exactly as directed. Misuse or overuse of OCUFLOX® could lead to the growth of bacteria that will not be killed by OCUFLOX® (resistance). This means that OCUFLOX® may not work for you in the future. Do not share your medicine.

What it does:

OCUFLOX® interferes with the bacterial enzyme responsible for growth and division, thereby helping stop the infection.

When it should not be used:

Do not use OCUFLOX® if you:

- Have a history of hypersensitivity to ofloxacin or to any of the ingredients of this medication (See **What the important nonmedicinal ingredients are**).
- Have a history of hypersensitivity to other quinolones.

What the medicinal ingredient is:

OCUFLOX® contains the antibiotic, ofloxacin, which is a member of the group of antibiotics known as "quinolones".

What the important nonmedicinal ingredients are:

Benzalkonium chloride 0.005% w/v (as preservative), sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust the pH, and purified water.

What dosage forms it comes in:

OCUFLOX® is supplied in plastic dropper bottles containing 5 mL.

WARNINGS AND PRECAUTIONS

This product should be used with caution in patients sensitive to other quinolone antibacterial agents.

Long term use may result in a new bacterial infection which does not respond to OCUFLOX®

This product should be used with caution in patients with a defect or damage to the surface of the eye.

Your sight may become blurred for a short time just after using OCUFLOX®. You should not drive or use machines until your sight is clear again.

BEFORE you use OCUFLOX® talk to your doctor or pharmacist if:

- Y ou are pregnant or intend to become pregnant.
- You are breastfeeding or planning to breastfeed
- You have any allergies to this drug, or to similar drugs (ask your doctor) or to OCUFLOX®'s ingredients or components of its container
- You wear contact lenses. The preservative in OCUFLOX® (benzalkonium chloride) may be absorbed by and discolour softcontact lenses. Lenses should be removed prior to application of OCUFLOX® and kept out for 15 minutes after use.

INTERACTIONS WITH THIS MEDICATION

Drug interaction studies have not been done for OCUFLOX®.

Tell your doctor or pharmacist if you are taking any other prescription or nonprescription (over-the-counter [OTC]) medicine, vitamins, herbals products.

PROPER USE OF THIS MEDICATION

Usual adult dose:

One to two drops every two to four hours for the first two days, and then four times daily in the affected eye(s) for 8 days.

How to Use:

1. Wash your hands. Tilt your head back and look at the ceiling.

1.

2. Gently pull the lower eyelid down until there is a small pocket.

2.

3. Turn the bottle upside down and squeeze it to release one or two drops into each eye that needs treatment.

3.

4. Let go of the lower lid, and close your eye for 30 seconds.

4.

If a drop misses your eye, try again.

To avoid contamination and injury, do not let the tip of the dropper touch your eye or anything else.

Replace and tighten the cap straight after use.

The proper application of your eye drops is very important. If you have any questions ask your doctor or pharmacist.

Overdose:

If you have placed too many drops in your eye(s), wash the eye(s) with clean water. Apply your next dose at the normal time.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should see your doctor if any of the following side effects that affect the eye(s) prove troublesome or if they are long lasting:

- temporary burning or discomfort
- irritation
- eye/eyelid swelling
- eye pain
- redness
- stinging
- itchy eye/eyelid
- tearing
- dryness
- light sensitivity
- blurred vision
- a feeling that something is in your eye

You should see your doctor if any of the following side effects that affect the body prove troublesome or if they are long-lasting:

- dizziness
- nausea
- swelling of the face

Stop OCUFLOX® use and contact your doctor if a severe allergic (hypersensitivity) reaction occurs with symptoms such as swelling of the mouth, throat, tongue or extremities (hands, feet), difficulty in breathing, skin reactions (redness, irritation , blistering, peeling), loss of consciousness or collapse.

This is not a complete list of side effects. For any unexpected effects while taking OCUFLOX®*, contact your doctor or pharmacist.*

HOW TO STORE IT

OCUFLOX® should be stored between 15° C to 25°C.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Allergan Inc. at: 1-877-255-3746

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