PRODUCT MONOGRAPH

[Pr]pms-OFLOXACIN

Ofloxacin Ophthalmic Solution USP

0.3%

Antibacterial Agent

PHARMASCIENCE INC.
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THERAPEUTIC CLASSIFICATION:

Antibacterial Agent

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

pms-OFLOXACIN (Ofloxacin) 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 influenzae

CONTRAINDICATIONS

pms-OFLOXACIN (Ofloxacin) 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.

WARNING

Ofloxacin is not for injection into the eye.

PRECAUTIONS

General

Prolonged use of Ofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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, dyspnea, 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.

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.

Use in Obstetrics

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, ofloxacin 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 ofloxacin in children have not been established.

Use in the Elderly

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 ofloxacin. 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

Ophthalmic Use of Ofloxacin

The most frequently reported drug-related adverse reaction was transient ocular burning or discomfort. Other reported reactions were ocular redness, stinging, itching, photophobia, tearing and dryness. One report of dizziness, one report of headache and one spontaneous report of toxic epidermal necrolysis 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 cranial 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. Photophobia was reported rarely in clinical trials with systemic ofloxacin and phototoxicity has been reported with other drugs in this class.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of accidental ingestion of 10 mL of ofloxacin, 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 ofloxacin 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 7 days, discontinue use and institute appropriate therapy.

Patients should be advised to avoid contamination of the dropper tip.

Use while wearing contact lenses:
The use of pms-OFLOXACIN (Ofloxacin) while wearing contact lenses has not been studied. Therefore, its use is not recommended while the lens is on the eye.

PHARMACEUTICAL INFORMATION

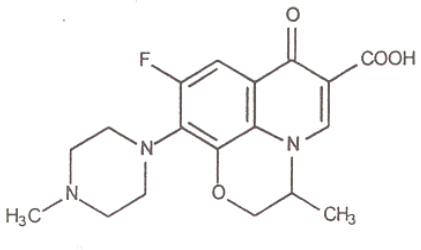
Drug Substance

Common Name: Ofloxacin (INN, USAN, BAN)

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

Structural Formula:



Molecular Weight: 361.37

Molecular Formula: $C_{18}H_{20}FN_3O_4$

Melting Point: 260-270°C (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

pms-OFLOXACIN (Ofloxacin) contains 0.3% ofloxacin with the following non-medicinal ingredients: benzalkonium chloride 0.005% (as preservative); sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust pH; and purified water.

Stability and Storage Recommendations

pms-OFLOXACIN is sterile in the unopened package. Store at 4° to 30°C.

AVAILABILITY OF DOSAGE FORMS

pms-OFLOXACIN (Ofloxacin) is available for topical ophthalmic administration as a 0.3% sterile solution, and is supplied in plastic Drop-Tainer® bottles containing 5 mL.

INFORMATION FOR THE CONSUMER

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.

Avoid contamination of the dropper tip.

Use while wearing contact lenses

The use of pms-OFLOXACIN (Ofloxacin) while wearing contact lenses has not been studied. Therefore, its use is not recommended while the lens is on the eye.

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	50.0
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 (C_{max}) 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	>1000
	F	5290	233	>1000
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.

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.

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, 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.
4	Monkey, cynomolgus 2 ½ 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.

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 peripheral 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	Initial No per Group	Dosages mg/kg/Day	Route	Duration	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. At 810 mg/kg/day, mortality, decrease in body weight gain, retardation of degree of ossification, increased incidence of skeletal variations such as cervical ribs and shortening of 13^{th} 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, 13-14, 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.
5	Rat, SD	24F	810, 1110, 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.	Days 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 to 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	Duration	Parameters	Major Findings
a	Rabbits, New Zealand albino	6F 6F 12F	1 gtt/16X/day Vehicle (OS) or 1 gtt/16X/day 0.3% Ofloxacin (OS) and Untreated control (OD)	7 days	Condition/ behaviour; Ocular damage; Body weight changes; Ocular irritation; Ophthalmoscopy	No ocular irritation, discomfort, toxicity or cytotoxicity. No abnormalities in the lens or retina.
b	Rabbits, New Zealand albino	6F 6F 12F	1 gtt/16X/day 0.5% Ofloxacin (OS) or 1 gtt/16X/day 1.0% Ofloxacin (OS) and Untreated control (OD)	7 days	Condition/ behaviour; Ocular irritation; Ocular/ corneal damage; Ophthalmoscopy; Body weight changes	Neither test solution caused ocular irritation, discomfort, toxicity nor cytotoxicity.

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
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/ behaviour; 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 Untreated control (OD)	33 days	Gross ocular observ.; Condition/ behaviour; Body weight changes; Ophthalmoscopy; Hematology; Blood chemistry; Histopathology; Ocular irritation; Ocular/ corneal damage;	Neither test solution caused systemic effects, ocular irritation, discomfort, toxicity or cytotoxicity

Table 7

Chronic Ocular Toxicity Studies

	Species, Strain	Initial No per Group	Ocular Dosage	Duration	Parameters	Major Findings
1	Rabbits, New Zealand albino	20M/20F 20M/20F 20M/20F 20M/20F 20M/20F 100M/100F	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) or 1 gtt/4X/day 1.0% Ofloxacin (OS) or Observed/4X/day Handled only and Untreated control (OD)	6 months	Condition/ behaviour; 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 nor cytotoxicity. No systemic treatment or dose related effect on general health, body weight, hematology, serum biochemistry, organ weight or histopathology.

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) 1 gtt/4X/day 0.5% Ofloxacin (OD) or 1 gtt/4X/day 1.0% Ofloxacin (OD) and Untreated control (OS)	6 months	Condition/ behaviour; Body weight changes; Ophthalmoscopy; Hematology; Blood chemistry; Urinalysis; Organ weights; Histopathology; Slit lamp examinations	No effect on general health, slit lamp, biomicroscopic 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 No per Group	Test Drug	Dosages mg/kg/day	Route	Duration	Major Findings
a	Rats, pigmented HOS; ACI/N 6 weeks	5M/ 5F	Ofloxacin Cinoxacin Chloroquine 0.5% CMC* (control)	100 100 80 10 mL	p.o.	4 weeks	Ofloxacin is not oculotoxic to pigmented rats. Abnormal respiratory behaviour observed sporadically in all test animals.
b	Rabbits, pigmented Rabbits, Japanese white albino	3 3	Ofloxacin 0.3% drop	1 gtt/3X/day	ocular	2 weeks	Ofloxacin may be bound to melanin-containing tissues such as iris/ ciliary body and retina/ choroid at relatively high concentrations, and be retained at low levels up to 9 weeks after multiple administration.
c	Bovine ocular melanin		Ofloxacin Chloroquine Befunolol Pilocarpine maleate Timolol maleate		in vitro		Melanin affinity of ofloxacin is less tan 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 No per Group	Test Drug	Dosages	Route	Duration	Major Findings
a	Dogs, Beagle	3M/3F	Ofloxacin	32 mg/kg/day	p.o.	3 weeks	After 21st daily dose, mean maximum ofloxacin concentrations (Cmax) 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 Rabbits, Japanese, white	3 3	Ofloxacin 0.3% eyedrop	1 gtt/3X/day	ocular	2 weeks	Mean ocular concentrations in pigmented rabbits 2 hours after the last dose were <0.32 µg/g in nictitating 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. Mean ocular concentrations in albino rabbits 2 hours after the last dose were <0.34 µg/g in nictitating 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. There was no great difference between albino and pigmented rabbits, except in iris/ ciliary body and retina/ choroid, in which pigmented rabbits had >5-fold higher ofloxacin concentrations.

c	Rabbits, albino	36F	Ofloxacin	0.12 mg/drop	ocular	1 drop	Mean ofloxacin Cmax (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
	Rabbits, albino	36F				5 drops/ 20 min	Mean Cmax (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 retina/ choroid.

ND* = Not detected

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