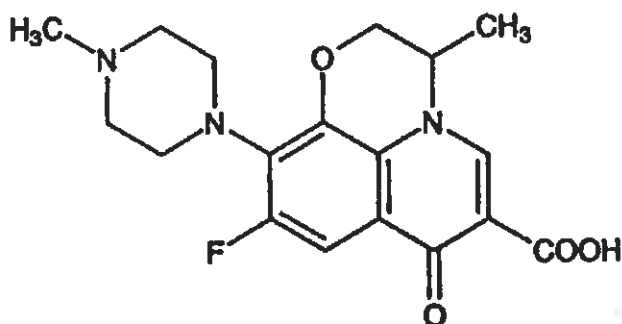


OCUFLOX®

Ofloxacin 3 mg/mL eye drops.

NAME OF THE DRUG

The active constituent of OCUFLOX® eye drops is ofloxacin.



(structure of ofloxacin)

CAS Registry No. J01MA01

DESCRIPTION

Ofloxacin is a white to yellow crystalline powder which is soluble in glacial acetic acid, sparingly soluble in chloroform and slightly soluble in water, methanol, ethanol or acetone. Its melting point is 260° - 270°C with decomposition.

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.

OCUFLOX® eye drops contain 3 mg/mL ofloxacin and are formulated as an isotonic solution using 9 mg/mL sodium chloride preserved with 0.05 mg/mL benzalkonium chloride. The pH of OCUFLOX® eye drops range from 6.0 - 7.0.

PHARMACOLOGY

Ofloxacin is a third generation fluorinated 4-quinolone having broad spectrum *in vitro* bactericidal activity against certain aerobic gram-positive, gram-negative and some anaerobic bacteria.

Ofloxacin appears to have more than one mechanism contributing to its bactericidal action. The primary mechanism of action is believed to be the inhibition of bacterial DNA gyrase, the enzyme responsible for inserting negative supercoils into bacterial DNA. Apparently, this enzyme inhibition leads to bacterial death through a complex process in which DNA synthesis is arrested and regulation of normal gene expression is disrupted. Ofloxacin, unlike most of the other quinolones, possesses an additional bactericidal mechanism which is not dependent on protein or RNA synthesis. It is bactericidal in both the replicating and nonreplicating stages of bacterial growth.

Ofloxacin, *in vitro* maintains an inhibitory effect on cell growth of susceptible bacteria for 6-8 hours after drug removal.

Ofloxacin is not subject to degradation by beta-lactamase enzymes nor is it modified by enzymes such as aminoglycoside adenylases or phosphorylases, or chloramphenicol acetyltransferase. Spontaneous resistance is rare and occurs in only 1 in 10^{10} to 10^{11} sensitive bacteria under routine laboratory conditions. Development of resistance to greater than 8 µg/mL of ofloxacin typically requires two independent genetic mutations under aerobic conditions. The viability and pathogenicity of most resistant mutants are reduced. Resistant mutants are typically unstable and most readily revert to full sensitivity to ofloxacin when cultured without quinolones.

Ofloxacin shows high selectivity for the bacterial DNA gyrase enzyme while showing little activity against mammalian topoisomerase (counterpart mammalian target) enzyme.

Cross-resistance has been observed between ofloxacin and other fluoroquinolones. Ofloxacin has shown *in vitro* efficacy against certain organisms resistant to other types of antimicrobials, including aminoglycosides, chloramphenicol, macrolides (erythromycin), sulfacetamide, penicillins and tetracycline.

Clinical Trials.

Corneal Ulcer: In a randomised, double-blind, parallel group trial of 134 patients with positive bacterial cultures, Ocuflax treated patients had an overall clinical success rate of 86%. The median time to clinical success was 11 days of treatment (range 8 - 14 days).

PHARMACOKINETICS

Serum, urine and tear film concentrations of ofloxacin were measured in 30 healthy women at various time points during a ten-day course of treatment with 3 mg/mL ofloxacin eye drops. 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 to 12 days. Maximum serum ofloxacin concentrations (1.89 ± 1.13 ng/mL) after ten days of topical dosing were more than 1000 times lower than those reported after standard oral doses of ofloxacin.

Topical ofloxacin was excreted in the urine primarily in unmodified form.

Tear film ofloxacin concentrations ranged from 5.67 to 31.0 µg/g during the 40-minute period following the last dose in the 11-day study. In 5 subjects mean tear film levels measured four hours after topical dosing (9.16 ± 8.24 µg/g) were higher than the 2 µg/mL minimum concentration of ofloxacin necessary to inhibit 90% of most bacterial strains (MIC_{90}) *in vitro*.

In rabbits, an eye-drop instillation produced therapeutically effective concentrations of ofloxacin in tears (ie above MIC_{90} for most ocular pathogens) for four to six hours.

INDICATIONS

OCUFLOX® eye drops are indicated for the treatment of corneal ulcers (bacterial keratitis) and severe bacterial conjunctivitis caused by ofloxacin sensitive organisms in adults.

CONTRAINDICATIONS

OCUFLOX® eye drops are contraindicated in patients sensitive to ofloxacin or any other component of the solution. A history of hypersensitivity to other quinolone anti-infectives, including nalidixic acid, may also contraindicate the use of OCUFLOX® eye drops.

PRECAUTIONS

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms. If superinfection occurs, or if clinical improvement is not noted within a reasonable period, discontinue use and institute appropriate therapy.

The use of OCUFLOX® eye drops while wearing contact lenses has not been studied. Contact lenses should not be worn during the period of treatment with OCUFLOX® eye drops.

OCUFLOX® eye drops are not for injection.

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) 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. Serious, acute hypersensitivity reactions may require immediate emergency treatment.

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

If an allergic reaction to ofloxacin occurs, discontinue the drug.

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

Quinolones induce phototoxicity in a number of *in vitro* and *in vivo* animal models. Quinolones have the potential to produce phototoxic reactions in sensitive individuals following systemic administration. Patients taking ofloxacin should avoid direct exposure to sunlight or artificial ultraviolet light. Therapy should be discontinued if photosensitivity occurs.

While systemic concentrations of ofloxacin are low following topical dosing, neurological adverse reactions (including convulsions, increased intra-cranial pressure and toxic psychosis) have been associated with oral administration.

Long-term, high dose use of other fluoroquinolones in experimental animals has caused lenticular opacities. However, this effect has not been reported in human patients, nor has it been noted following topical ophthalmic treatment with ofloxacin for up to six months in animal studies including studies in monkeys.

Carcinogenicity: Long term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Use in pregnancy: (Category B3). There were no adequate and well-controlled studies performed in pregnant women. Since systemic quinolones have been shown to cause arthropathy in immature animals, it is recommended that OCUFLOX® eye drops not be used in pregnant women.

Ofloxacin has not been shown to have any teratogenic effects at oral dose up to 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day demonstrated no adverse effects on late foetal development, labour, 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.

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

Use in children: Adequate clinical studies of the safety of topical ophthalmic treatment with ofloxacin in children have not been conducted. OCUFLOX® eye drops should be avoided in children who have not attained joint maturity. The oral administration of quinolones (including norfloxacin, ciprofloxacin, ofloxacin, nalidixic acid and cinoxacin) has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Use in elderly: No comparative data are available with topical dosing in elderly versus other age groups.

Interactions with other drugs: It has been shown that the systemic administration of some quinolones inhibits the metabolic clearance of caffeine and theophylline. Drug interaction studies conducted with systemic ofloxacin have demonstrated that metabolic clearance of caffeine and theophylline are not significantly affected by ofloxacin.

Although there have been reports of an increased prevalence of CNS toxicity with systemic dosing of fluoroquinolones when used concomitantly with systemic nonsteroidal anti-inflammatory drugs (NSAIDs), this has not been reported with the concomitant systemic use of NSAIDs and ofloxacin.

ADVERSE REACTIONS

The following adverse reactions have been reported in association with use of ofloxacin.

Transient side effects reported with OCUFLOX® eye drops include burning/stinging (10-14% of treated eyes), tearing (6-11% of treated eyes), itching, foreign body sensation, photophobia, blurred vision, hyperemia, conjunctivitis, chemical conjunctivitis/keratitis, periocular/facial oedema, eye oedema, eye pruritus, eyelid pruritus, dry eyes, eye pain (1-5% of treated eyes) and dizziness. These symptoms led to cessation of treatment in 1.6% of patients.

Adverse events such as burning and stinging, tearing, photophobia and foreign body sensation occur more frequently in patients treated for corneal ulcer. The incidence of discomfort is likely to be a result of the underlying condition.

Gastrointestinal disorders reported include nausea.

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

DOSAGE AND ADMINISTRATION

Corneal Ulcers (bacterial keratitis):

Days 1 and 2: Instill one to two drops into the affected eye(s) every 30 minutes while awake. Instill a further one to two drops into the affected eye(s) during the night, four hours after retiring, and again two hours after this.

Days 3 to 7: Instill one to two drops into the affected eye(s) every hour while awake.

Days 7 to completion of treatment (usually within 21 days): Instill one to two drops into the affected eye(s) four times daily until the ulcer is completely healed (complete epithelialisation and no progression of infiltrate).

Bacterial Conjunctivitis:

The dosage recommendation is one drop every four hours for the first two days, and then one drop every six hours into the affected eye(s) for up to eight days. Dosage should not normally be continued for more than 10 days without an ophthalmic review (see Precautions).

In order to minimise systemic absorption of OCUFLOX[®] eye drops, apply pressure to the tear duct immediately following administration of the drug.

OCUFLOX[®] eye drops have been assessed in clinical studies for up to 23 days treatment; safety has not been adequately demonstrated for longer periods of use.

OVERDOSAGE

The acute oral LD₅₀ values in male/female mice and male/female rats exceed 5 g/kg and 3 g/kg respectively. In monkeys, the acute oral LD₅₀ value is greater than 0.5 g/kg. Acute overdosage information for humans is not available.

Signs of toxicity after oral or subcutaneous administration included hypoactivity, ptosis, hypopnoea, convulsion and tremor in rats, mice, dogs and monkeys. In addition, emesis was observed in dogs and monkeys.

In the event of accidental ingestion of 5 mL of OCUFLOX[®] eye drops, 15 mg of ofloxacin would be ingested. This amount does not appear to be clinically significant in terms of overdosage. However, there would be an increased potential for systemic reactions (see **Adverse Effects**).

In the event of a topical overdosage, flush eye with a sterile topical ocular irrigant.

PRESENTATION

Eye drops: 5 mL (dropper bottle).
Storage: Store below 25°C. Protect from light and excessive heat.
Shelf life: 2 years.

To avoid contamination of the solution, keep container tightly closed.

Do not touch dropper tip to any surface.

Discard contents 4 weeks after opening the bottle.

Contents are sterile if seal is intact.

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