

DATA SHEET

NAME OF MEDICINE

OCUFLOX

Allergan New Zealand Ltd

Ofloxacin 0.3% (3mg/mL)

PRESENTATION

Ocuflox is a sterile ophthalmic solution containing ofloxacin 0.3% benzalkonium chloride (0.005%), sodium chloride and purified water. The formulation may also contain hydrochloric acid or sodium hydroxide to adjust pH.

USES

ACTIONS

Ofloxacin appears to have more than one mechanism contributing to its bacterial 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 rapid bacterial death through a complex process in which DNA synthesis is rapidly 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's bactericidal action is fast, with 90% of most bacteria killed in 19-55 minutes. It also maintains an inhibitory effect on cell growth of susceptible bacteria for 6-8 hours after drug removal.

Plasmid-mediated bacterial resistance to ofloxacin has not been reported to date. 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 $\mu\text{g}/\text{mL}$ 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.

Ofloxacin has been shown to be effective against the following organisms isolated from lids or conjunctiva in clinical studies (and *in vivo*).

Gram-Positive Cocci: *Micrococcus sp*, *Staphylococcus sp* including, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococcus sp* including *Streptococcus pneumoniae*, *Streptococcus viridans*, beta hemolytic *Streptococcus*

Gram-Positive Bacilli: *Bacillus sp*, *Corynebacterium sp*.

Gram-Negative Cocci: *Neisseria sp*

Gram-Negative Bacilli: *Acinetobacter calcoaceticus* including: *Acinetobacter c.var. anitratum*, *Acinetobacter c. var. Iwoffi*.

Enterobacter sp including: *Enterobacter cloacae*.

Haemophilus sp including: *Haemophilus influenza*, *Haemophilus aegyptius*, (*Kock-Weeks bacillus*)

Klebsiella sp including: *Klebsiella pneumoniae*.

Moraxella sp (*Morax-Axenfeld bacillus*). *Morganella morganii*

Proteus sp including: *Proteus mirabilis*

Pseudomonas sp including: *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Pseudomonas fluorescens*

Serratia sp including: *Serratia marcescens*

Ofloxacin has been shown to have *in vitro* activity against the following organisms although clinical efficacy has not been documented. The levels of drug achieved in the tears 30 minutes to 4 hours in humans and 30 minutes to 6 hours in rabbits after topical dosing is typically higher (see Pharmacokinetics) than the MIC's for the majority of these organisms.

Gram-Positive Cocci: *Streptococcus agalactiae*, *Streptococcus aveum*, *Streptococcus bovis*, *Streptococcus faecalis*, *Streptococcus intermedius*, *Streptococcus laecalis*, *Streptococcus mitis*, *Streptococcus pyrogenes*, *Streptococcus sanguis*, *Streptococcus salivarius*.

Gram-Positive Bacilli: *Listeria monocytogenes*, *Nocardia sp*

Gram-Negative Cocci: *Branhamella catarrhalis*, *Neisseria gonorrhoeae*

Gram-Negative Bacilli: *Achromobacter group*, *Achromobacter xylosoxidans*, *Aeromonas hydrophilia*, *Agrobacterium radiobacter*, *Alcaligenes dentrificans*, *Alcaligenes faecalis*, CDC group VE-2, CDC group IIB, CDC group IV C-2, *Citrobacter sp* including: *Citrobacter amalomerans*, *Citrobacter diversus*, *Citrobacter freundii*, *Eikeneila corrodens*, *Enterobacter aerogenes*, *Enterobacter agglomerans*, *Enterobacter amingenus biogroup II*; *Escherichia coli*, *Flavobacterium sp* including: *flavobacterium meningosepticum*, *Flavobacterium multivorum* *Haemophilis hemolyticus*, *Haemophilis parainfluenzae (bio II)*, *Haemophilis parainfluenzae (bio III)*, *Klebsiella oxytoca*, *Klebsiella ozaenae*, *Moraxella lacunata*, *Moraxella nonliquifaciens (rough)*, *Moraxella nonliquifaciens (smooth)*, *Proteus inconstans*, *Proteus morganii*, *Proteus vulgaris*, *Providencia sp* including: *Providencia stuartii*

Pseudomonas acidomni, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas diminuta*, *Pseudomonas maltophilis*, *Pseudomonas mesophilia*, *Pseudomonas paucimobilis*, *Pseudomonas pickertiti*, *Pseudomonas putida*, *Pseudomonas putrifaciens*, *v stutzeri*, *Pseudomonas vesicularis*, *Serratia liquifaciens*, *Serratia odorani*, *Shigella sonnel*.

Anaerobic Bacteria: *Propionibacterium acnes*, *Clostridium sp*

Chlamydia trachomatis

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 0.3% ofloxacin eye drops. Maximum serum ofloxacin concentrations after ten days of topical dosing were more than 1000 times lower than those reported after standard oral doses of ofloxacin, and no systemic side effects attributable to topical ofloxacin were observed.

Topical ofloxacin was excreted in the urine primarily in unmodified form. Tear film ofloxacin concentrations ranged from 5.67 to 31.0 $\mu\text{g/g}$ during the 40 minute period following the last dose on Day 11. Mean tear film levels measured four hours after topical dosing (9.16 $\mu\text{g/g}$) were higher than the 2 $\mu\text{g/mL}$ minimum concentration of ofloxacin necessary to inhibit 90% of most bacterial strains (MIC_{90} *in vitro*). The ability to achieve and maintain tear ofloxacin

levels higher than the MIC₉₀ for at least 4 hours after topical application may help account for the clinical efficacy of ofloxacin in treating external ocular infections.

Ofloxacin 0.3% was administered topically to humans 5 times daily for 2 days followed by 5 doses at 5 minute intervals. The mean aqueous humor concentrations were 1.2 and 1.7 µg/mL at 60 and 120 minutes respectively post-instillation.

In another human study, dosing 3 times at 5 minute intervals prior to surgery resulted in mean aqueous humor concentrations of 0.5 to 0.8 µg/mL between 30 and 180 minutes after topical dosing.

Ofloxacin 0.3% applied topically to rabbit eyes 5 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 none in the serum one hour after Instillation.

Single dose topical administration in rabbit eyes resulted in tear concentrations beginning at 2207 µg/gm and declining to 34 µg/gm 20 minutes post-dosing. The tear concentration was 2.5 µg/gm 6 hours post dosing. Ofloxacin maintained therapeutically effective tear concentrations throughout the 6 hour period while the aminoglycosides (gentamicin and tobramycin) did not.

INDICATIONS

Ocuflox is indicated for the treatment of external ocular infections in adults and children that are caused by ofloxacin-sensitive organisms.

Treatable infections include conjunctivitis, blepharitis, blepharoconjunctivitis, keratoconjunctivitis, dacryocystitis, keratitis, meibomianitis and hordeolum. Ocuflox can also be used to help prevent postoperative infection.

Ofloxacin has shown *in vitro* efficacy against certain organisms resistant to other types of antimicrobials, including aminoglycosides, chloramphenicol, macrolides (erythromycin), sulfacetamide, penicillins, and tetracycline. The most likely explanation for this effect is the different mechanism of action demonstrated by ofloxacin.

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). Dosage should not normally be continued for more than 10 days without an ophthalmic review.

As part of a pre-operative regimen, Ocuflox should be instilled 5 times daily beginning 2 days prior to surgery, with additional drops instilled in the immediate 1 to 2 hours prior to surgery.

CONTRAINDICATIONS

Ocuflox is contraindicated in patients sensitive to ofloxacin or any of its components.

WARNINGS AND PRECAUTIONS

Ocuflox is not for injection.

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

Use Ocuflax with caution in patients who have exhibited sensitivities to other quinolone antibacterial agents.

Pregnancy: 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 Ocuflax not be used in pregnant women.

Nursing Mothers: 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.

ADVERSE EFFECTS

Transient ocular irritation (burning, stinging, redness, itching or photophobia) was reported in clinical trials in 22 patients out of 1373 (1.6%). One report of dizziness with numbness and nausea, one report of dizziness alone, one report of headache, and one report of haemorrhagic conjunctivitis with palpebral oedema due to an allergic reaction were received from the same patient population.

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

INTERACTIONS

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.

OVERDOSAGE

Acute overdose 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 10mL of Ocuflax, 30mg of ofloxacin would be ingested. This amount does not appear to be clinically significant in terms of overdose. However, there would be an increased potential for systemic reactions.

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

PHARMACEUTICAL PRECAUTIONS

Store at controlled room temperature, 15 -30°C

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Ocuflox is supplied sterile in dropper bottles of 5mL and 10mL

FURTHER INFORMATION

Susceptibility tests: Reports from the laboratory giving results of the standard single disc susceptibility test with a 5mcg ofloxacin disc should be interpreted according to the following criteria:

Susceptible organisms produce zones of 16 mm or greater, indicating that the test organism is likely to respond to therapy. Organisms showing intermediate susceptibility produce zones greater than 12 to less than 16 mm, indicating that the test organism may respond to therapy. Resistant organisms produce zones of 12 mm or less.

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