AUSTRALIAN PRODUCT INFORMATION – OCUFLOX® (OFLOXACIN) EYE DROPS

1 NAME OF THE MEDICINE

Ofloxacin.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OCUFLOX® eye drops contain 3 mg/mL ofloxacin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops, solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 Section 4.4 Special Warnings and Precautions for Use).

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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

The preservative in OCUFLOX® eye drops, benzalkonium chloride, may be absorbed by and cause discoloration of soft contact lenses. OCUFLOX® eye drops should not be administered while wearing soft contact lenses. Patients should be instructed to remove contact lenses prior to the administration of OCUFLOX® and wait at least 15 minutes following administration before reinserting 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.

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. Oxygen and airway management should be administered as clinically indicated.

There have been rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis reported in association with topical ophthalmic ofloxacin.

Hypersensitivity reactions including angioedema, dyspnea, anaphylactic reaction/shock, oropharyngeal swelling, and tongue swollen have been reported with OCUFLOX® eye drops (see Section 4.8 Adverse Effects (Undesirable Effects) - Postmarketing Experience).

If an allergic reaction to ofloxacin occurs, discontinue the drug. Use OCUFLOX® eye drops with caution in patients who have exhibited sensitivities to other quinolone antibacterial agents.

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.

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.

Use in the elderly

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

Paediatric use

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.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Post marketing experience

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

Eye disorders

Hypersensitivity, lacrimation increased, eyelid oedema and ocular hyperemia.

Immune system disorders

Hypersensitivity (including angioedema, dyspnea, anaphylactic reaction/shock, oropharyngeal

swelling and tongue swollen) and allergic dermatitis.

Nervous system disorders

Dizziness

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The acute oral LD_{50} values in male/female mice and male/female rats exceed 5 g/kg and 3 g/kg respectively. In monkeys, the acute oral LD_{50} 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 Section 4.8 Adverse Effects (Undesirable Effects)).

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials

Corneal Ulcer: In a randomised, double-blind, parallel group trial of 134 patients with positive bacterial cultures, Ocuflox 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).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.*

Distribution

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

Metabolism

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.

Excretion

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light and excessive heat.
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.

6.5 NATURE AND CONTENTS OF CONTAINER

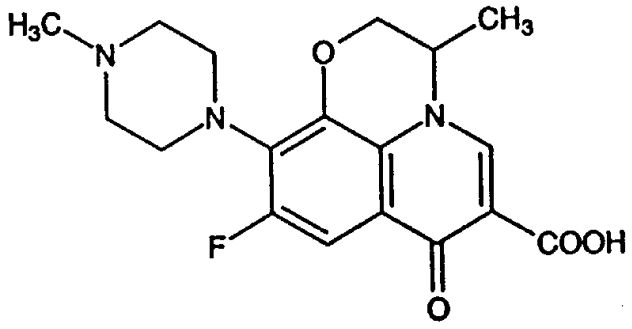
Eye drops: 5 mL (dropper bottle). AUST R 47485

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



(Structure of ofloxacin)

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.

CAS number: 82419-36-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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Ph: 1800 043 460
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9 DATE OF FIRST APPROVAL

2 December 1997

10 DATE OF REVISION

23 August 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Update to Sponsor details.