SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OFLOX Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 3.0 mg ofloxacin (0.3% w/v).

Excipient with known effect:
Each ml of solution contains 0.05mg of benzalkonium chloride (0.005% w/v).
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Ophthalmic, solution
Clear, pale to light yellow-green solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

OFLOX is indicated for the topical treatment of external ocular infections caused by ofloxacin-sensitive organisms.

4.2 Posology and Method of Administration

Adults only: One to two drops in the affected eye(s) three or four times daily. The length of treatment should not exceed 10 days without an ophthalmic review.

4.3 Contraindications

OFLOX is contra-indicated in individuals who have shown hypersensitivity to ofloxacin, any of its excipients listed in section 6.1, or any other quinolones. OFLOX is not recommended for use in children or adolescents before epiphyseal closures.
OFLOX should not be used during pregnancy or in women at risk of pregnancy, nor during lactation.

4.4 Special Warnings and Precautions for Use

OFLOX is 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 oedema), airway obstruction, dyspnoea, urticaria, and itching.

If an allergic reaction to ofloxacin occurs, discontinue the drug. Use OFLOX with caution in patients who have exhibited sensitivities to other quinolones antibacterial agents.

When using OFLOX eye drops the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance should be considered. As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms. If infection worsens, or if clinical improvement is not noted within a reasonable period, discontinue use and institute alternative therapy.

Data are very limited to establish efficacy and safety of ofloxacin eye drops 0.3% in the treatment of conjunctivitis in neonates.

The use of ofloxacin eye drops in neonates with ophthalmia neonatorum caused by Neisseria gonorrhoeae or Chlamydia trachomatis is not recommended as it has not been evaluated in such patients.

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

The following precautions are relevant for the systemic absorption of oxoquinolone antibacterial agents. However, the plasma levels of ofloxacin following absorption from topically applied OFLOX eye drops are minimal.

Patients with pre-existent significant renal or hepatic disorders should be carefully monitored to detect any deterioration in function. Dosage reduction may be required.

OFLOX should be administered with caution to persons with existent central nervous system disorders, epilepsy, hepatic or renal insufficiency, or severe dehydration. Photosensitivity reactions may be induced. Evidence of CNS irritability has been reported particularly in the elderly, leading occasionally to psychosis.

Clinical and non-clinical publications have reported the occurrence of corneal perforation in patients with pre-existing corneal epithelial defect or corneal ulcer, when treated with topical fluoroquinolone antibiotics. However, significant confounding factors were involved in many of these reports, including advanced age, presence of large ulcers, concomitant ocular conditions (e.g. severe dry eye), systemic inflammatory diseases (e.g. rheumatoid arthritis), and concomitant use of ocular steroids or non-steroidal anti-inflammatory drugs. Nevertheless, it is necessary to advise caution regarding the risk of corneal perforation when using product to treat patients with corneal epithelial defects or corneal ulcers.

Corneal precipitates have been reported during treatment with topical ophthalmic ofloxacin. However, a causal relationship has not been established.

Caution should be taken when using fluoroquinolones, including OFLOX, in patients with known risk factors for prolongation of the QT interval such as, for

example:
- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including OFLOX, in these populations.

(see section 4.2 elderly, section 4.5, section 4.8, section 4.9)

OFLOX contains the preservative benzalkonium chloride which may cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. OFLOX should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Patients should be monitored in case of prolonged use.

Use of contact lenses is not recommended in patients receiving treatment for an eye infection. Patients should remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

Sun or UV- exposure should be avoided during use of ofloxacin due to the potential for photosensitivity.

4.5 Interaction with other medicinal products 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.

Mineral antacids used simultaneously may effect systemic absorption. Concomitant use of systemic quinolones with some phenylproprionic acid derived non-steroidal anti-inflammatory drugs may lead to toxicity possibly because of renal effects.
A study of concurrent administration with a coumarin anticoagulant showed no interaction.

OFLOX, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti- arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4)

4.6 Pregnancy and Lactation

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, it is recommended that OFLOX should not be used in pregnant women.

Breastfeeding

Because ofloxacin and other quinolones taken systemically are excreted in breast milk and there is potential for harm to nursing infants, OFLOX should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Transient blurring of vision may occur on instillation of eye drops. Do not drive or operate hazardous machinery unless vision is clear.

4.8 Undesirable Effects

General
Serious reactions after use of systemic ofloxacin are rare and most symptoms are reversible. Since a small amount of ofloxacin is systemically absorbed after topical administration, adverse events reported with systemic use could possibly occur.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following terminologies have been used in order to classify the occurrence of undesirable effects: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Immune System Disorders:
Not known: Hypersensitivity reaction including signs or symptoms of Eye allergy (such as Eye pruritus and Eyelid pruritus) and Anaphylactic reactions (such as angioedema, dyspnea, anaphylactic shock, oropharyngeal swelling, facial oedema and tongue swollen)

Nervous System Disorders:
Not known: Dizziness
Headache
Hypoaesthesia

Eye Disorders:

Common: Eye irritation
Ocular discomfort

Not known: Keratitis
Conjunctivitis
Vision blurred
Photophobia
Foreign body sensation in eyes
Lacrimation increased
Dry eye
Eye pain
Ocular hyperaemia
Periorbital oedema (including eyelid oedema)

Cardiac disorders:
Not known: ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9)

Gastrointestinal Disorders:
Not known: Nausea

Skin and Subcutaneous Tissue Disorders:
Not known: Stevens-Johnson syndrome
Toxic epidermal necrolysis

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 Overdose

No case of overdose has been reported.

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

In the event of an overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, anti-infectives, fluoroquinolones

ATC code: S01AE01.

Ofloxacin is a synthetic fluorinated 4-quinolone, having fast acting, broad spectrum bactericidal activity against certain aerobic gram-positive and gram- negative bacteria.

Ofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and clinically in ophthalmic infections. Clinical trial evidence of the efficacy of OFLOX against *S. pneumoniae* was based on a limited number of isolates.

Gram-negative bacteria: *Acinetobacter calcoaceticus var. anitratum and A. calcoaceticus var. lwoffi; Enterobacter sp. including E. cloacea, Haemophilus sp. including H. influenza and H. aegyptius; Klebsiella sp. including K. pneumoniae; Moraxella sp; Morganella morganii; proteus sp. including P. mirabilis; Pseudomonas sp. including P. aeruginosa, P. cepacia, and P. fluoroscens; and Serrata sp. including S. marcescens.*

Gram-positive bacteria: *Bacillus sp; Corynebacterium sp; Micrococcus sp; Staphylococcus sp. including S. aureus and S. epidermidis; Streptococcus sp. including S. pneumoniae (see above), S. viridans and beta-haemolytic Streptococcus.*

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 bactericidal DNA gyrase, the enzyme responsible for inserting negative supercoils into bacterial DNA. This inhibition causes the rapid death of bacteria by stopping DNA replication, which apparently induces a cellular response leading to further damage to bacterial DNA and preventing normal gene expression. In addition, ofloxacin possesses an additional bactericidal mechanism which is independent of protein and DNA synthesis. Therefore it is bactericidal in both the replicating and non-replicating stages of growth. Mammalian cells are not inhibited by the quinolones.

5.2 Pharmacokinetic Properties

After ophthalmic instillation as an eyedrop, ofloxacin is well absorbed and distributed to all parts of the eye.

In a healthy volunteer study, mean tear film concentrations of ofloxacin measured four hours after topical dosing (9.2 mcg/ml were higher than the 2 mcg/ml) minimum concentration of ofloxacin necessary to inhibit 90% of most ocular bacterial strains (MIC_{90}) *in vitro*.

Systemically absorbed ofloxacin is widely distributed and undergoes rapid elimination from the body. It is mainly excreted unchanged in the urine.
The maximal serum concentration observed after ophthalmic doses to man (approx.1.9 ng/ml) was at least two thousand fold lower than that after an oral 300 mg dose(approx. 4625 ng/ml).

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.

5.3 Preclinical Safety Data

Systemic toxicity studies have been conducted in a number of animals species at acute, subacute and chronic levels using a variety of experimental animals. The choices were consistent with general practices in drug investigation. Reproduction studies including fertility and teratogenicity have also been carried out. Together these have established the safety of the drug.

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.

The profile of ofloxacin compares favourably with those of other wide-spectrum antimicrobial agents. The much lower dosages used ophthalmically result in less drug absorption and far fewer adverse events are expected with this mode of administration.

The main effects noted have been primarily gastrointestinal complaints with some central nervous effects. However, the most notable effect has been the action of ofloxacin on articular cartilage in immature animals and in this respect the product is not recommended during pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Benzalkonium chloride
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years, unopened.
Discard unused contents 28 days after opening the bottle.

6.4 Special Precautions for Storage

Do not store above 25ºC.

6.5 Nature and Contents of Container

Low density polyethylene (LDPE) bottle with LDPE tip and medium or high impact polystyrene cap. Contains 5 ml in a 10 ml bottle.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport Co.
Mayo Ireland

8. REGISTRATION HOLDER

Allergan Israel Ltd., 32 Shacham street, POB 6869, Petach-Tikva.

9. MARKETING AUTHORISATION NUMBER

117-23-27973-00

10. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorization: 01/10/1994

11. DATE OF REVISION OF THE TEXT

Revised in May 2021 according to MOHs guidelines