SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLOXAL®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: ofloxacin
1 g eye ointment contains 3 mg of ofloxacin. One single dose (a strip of the eye ointment with length of 1 cm) contains 0.12 mg of ofloxacin.

Excipients with known effect: wool fat (lanolin)
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye ointment
Light yellowish ointment with soft consistency

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections of the anterior eye section with ofloxacin-sensitive pathogens: chronic conjunctivitis, keratitis and corneal ulcers, and chlamydia infections.

4.2 Posology and method of administration

Posology
Unless otherwise prescribed, insert a strip with length of 1 cm (equivalent to 0.12 mg of ofloxacin) three times daily (in chlamydia infections five times daily).

The length of treatment should not exceed 14 days.

Notice: If different topical ocular medications are used concomitantly, at least a 15-minute interval is required between applications. Floxal® should always be applied last.

Method of administration
For topical ocular use

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or any other quinolones.

4.4 Special warnings and precautions for use

Ofloxacin is not intended for injection.

Safety and effectiveness in infants below the age of one year have not been established.

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 Floxal® with caution in patients who have exhibited sensitivities to other quinolone antibacterial agents.

When using ophthalmologicals containing ofloxacin, 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 worsening infection occurs, 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 0.3% ofloxacin ophthalmologicals in the treatment of conjunctivitis in neonates.

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

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 this medicinal product to treat patients with corneal epithelial defects or corneal ulcers.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ofloxacin, particularly in older patients and those treated concurrently with corticosteroids.

Therefore, caution should be exercised and treatment with Floxal® should be discontinued at the first sign of tendon inflammation (see section 4.8).

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

Excessive sun or UV-exposition (e. g. sunlamp, solarium etc.) should be avoided during use of ofloxacin (potential for photosensitivity).

Use of contact lenses is not recommended in patients receiving treatment for an eye infection.

Wool fat (lanolin) is known to cause localised skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

It has been shown that 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 is 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 Pregnancy and lactation

Pregnancy
There have been no adequate studies on ofloxacin performed in pregnant women. Since systemic quinolones have been shown to cause arthropathy in immature animals, it is recommended that ofloxacin should not be used during pregnancy.

Breastfeeding
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

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

Transient blurring of vision for only a few minutes may occur through formation of streaks at insertion of eye ointment in the conjunctival sac. Do not drive, operate machinery or work without a secure hold 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, side effects reported with systemic use could possibly occur.

Adverse reactions have been ranked under headings of frequency using the following convention:
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 available data).

Frequency / **System organ class**	**Common**	**Rare**	**Very rare**	**Not known**
Immune system disorders			Hypersensitivity (including angioedema, dyspnoea, anaphylactic reaction/ anaphylactic shock, oropharyngeal swelling and swollen tongue).	
Nervous system disorders				Dizziness
Eye disorders	Eye irritation; mild eye pain	Corneal precipitates, especially in pre-existing corneal disorders		Keratitis; conjunctivitis; blurred vision; photophobia; eye oedema; foreign body sensation in the eyes; increased lacrimation; dry eye; eye pain, ocular hyperaemia, hypersensitivity (including eye pruritus and eyelid pruritus), periorbital oedema

				(including eyelid oedema). Hypersensitivity reactions in the form of conjunctival redness and/or mild burning in the treated eye are possible. However, these symptoms are usually short term.
Gastrointestinal tract disorders				Nausea
Skin and subcutaneous tissue disorders				Periorbital oedema, facial oedema, Stevens-Johnson syndrome, toxic epidermal necrolysis

Tendon ruptures of the shoulder, hand, Achilles' heel, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ophthalmologicals, anti-infectives
ATC code: S01AE01

Mechanism of action
The derivative of quinolinic acid, ofloxacin, is a gyrase inhibitor with bactericidal effect.

Breakpoints
In the resistance study mentioned below, ofloxacin was tested using the commonly applied dilution series. The following minimum inhibitory concentrations (MICs) have been determined for susceptible and resistant agents.

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints:

Agent	Susceptible	Resistant
Enterobacteriaceae	≤0.5 mg/l	>1 mg/l
Staphylococcus spp.	≤1 mg/l	>1 mg/l
Streptococcus pneumoniae	≤0.125 mg/l	>4 mg/l
Haemophilus influenzae	≤0.5 mg/l	>0.5 mg/l
Moraxella catarrhalis	≤0.5 mg/l	>0.5 mg/l
Neisseria gonorrhoeae	≤0.12 mg/l	>0.25 mg/l
No species-specific breakpoints *	≤0.5 mg/l	>1 mg/l

* Primarily based on serum pharmacokinetics

Antibacterial spectrum
The antibacterial spectrum of ofloxacin includes fastidious anaerobes, facultative anaerobes, aerobes and other germs, such as, for example, chlamydia.
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. If necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ofloxacin in infections is questionable.
Especially in severe infections or lack of efficacy a microbiological diagnosis with detection of the pathological germ and its sensitivity to ofloxacin should be done. A cross resistance of ofloxacin with other fluoroquinolones may occur.

Resistance data presented in the table below are mainly based on current results of a study on the prevalence of resistance among 1391 bacterial isolates obtained from patients with eye infections (predominantly external smears) in 31 German centres. Data are based on the above breakpoints for systemic use. Topical application of ofloxacin to the eye usually achieves much higher antibiotic concentrations in the anterior eye segment than by systemic route. Therefore, clinical efficacy for approved indications may also be achieved with agents, such as.
B. Enterococcus spp., being defined as resistant in the in vitro resistance determination.

Commonly susceptible species

Aerobic Gram-positive-microorganisms
Bacillus spp.
Staphylococcus aureus (methicillin-susceptible)

Aerobic Gram-negative microorganisms
Acinetobacter baumannii
Acinetobacter lwoffi
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae

Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis
Serratia marcescens

Species for which acquired resistance may pose a problem during treatment

Aerobic Gram-positive microorganisms
Corynebacterium spp.
Enterococcus faecalis
Staphylococcus aureus (methicillin-susceptible) +
Staphylococcus epidermidis
Streptococcus pneumoniae $
Streptococci (except *Streptococcus pneumoniae*) $

Aerobic Gram-negative microorganisms
Pseudomonas aeruginosa
Stenotrophomonas maltophilia

Inherently resistant species

Aerobic Gram-positive microorganisms
Enterococcus spp.

$ The natural susceptibility of most bacterial isolates to a given antibiotic is said to be intermediate. However, concentrations of at least 4 mg/l have been seen in the tear film for four hours following a single application, which reliably kills 100% of the isolates.
+ In at least one area, the resistance rate is over 50%.

5.2 Pharmacokinetic properties

The efficacy primarily depends on the ratio of maximum tissue concentration (Cmax) and minimal inhibitory concentration (MIC) of the pathogen.

Non-clinical studies revealed evidence that ofloxacin applied topically has been detected in the cornea, conjunctiva, eye muscle, sclera, iris, ciliary body and anterior chamber. Repeated application also led to therapeutic concentrations in the vitreous.
Following a single dosing of ointment strip with length of approx. 1 cm (equivalent to 0.12 mg ofloxacin), concentrations of 9.72 µg/g in the cornea and 1.61 µg/g in the sclera reached maximum levels five minutes post-dose. Concentration values then decreased slowly. Aqueous humour and corneal concentrations measured maximum levels of 0.69 µg/g and 4.87µg/g one hour post-dose.

5.3 Preclinical safety data

There were no toxicological safety issues with ofloxacin from topical ocular administration. Local safety of Floxal® proved to be good. A 16 times dose administration over 8 hours may cause vascular injection and conjunctival swelling.
Several in-vitro- and in-vivo-tests for induction of gene- and chromosome mutations were negative. Long-term animal studies for carcinogenicity have not been performed. There is no evidence for a cataractogenic or co-cataractogenic effect. Ofloxacin has no influence on fertility, peri- and post-natal development and is non-teratogenic. Following systemic administration of ofloxacin to test animals, degenerative changes to the articular cartilage have been observed. The articular cartilage damages that occurred were dose-dependent and age-related.
(The younger the animal, the more pronounced the damages were.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White petrolatum, liquid paraffin and wool fat (lanolin).

6.2 Incompatibilities

No studies have been conducted.

6.3 Shelf life

The expiry date is indicated on the packaging materials.
Do not use for longer than 6 weeks after opening.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Polyfoil tube (white) made of polyfoil tube laminate 405 with HDPE tube tip (white) and HDPE screw cap (white).

Original pack: 1 tube with 3 g of eye ointment.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. REGISTRATION NUMBER

165-34-35520-00

8. MANUFACTURER

Dr. Gerhard Mann
chem.-pharm. Fabrik GmbH
Brunsbutteler Damm 165/173
Berlin, Germany.

9. LICENCE HOLDER

Fischer Pharma RX Ltd.
7 Hamasger St., Or Yehuda 6022307

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