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SCOTT-EDIL PHARMACIA LTD.

56, E.P.I.P Phase –I, Jharmajri, Baddi, Distt. Solan-173205 (HP) , India

Summary of Product Characteristics (SPC)

1. Name of the medicinal product
TINOVID (Ofloxacin Eye/Ear Drops 0.3% w/v)

1.1 *International Non-Proprietary Name (INN)*
Ofloxacin Eye/Ear Drops 0.3% w/v

1.2 *Strength*
0.3%w/v

1.3 *Pharmaceutical form*
Ophthalmic Solution, 0.3%

2. Qualitative and quantitative composition
Each ml contains:
Ofloxacin BP …..... 0.3% w/v
Hydroxypropyl Methyl Cellulose BP …….. 0.25% w/v
Benzalkonium Chloride BP …..... 0.02% w/v
(As Preservative)
Aqueous Buffered vehicle …..... q.s.

3. Pharmaceutical form
Ophthalmic Solution, 0.3%

4. Clinical particulars
4.1 Therapeutic indications

Ofloxacin Eye/Ear Drops are indicated for the treatment of ocular infections caused by susceptible strains of the following bacteria in the conditions listed below:

Conjunctivitis

Gram-positive Bacteria	***Gram-negative Bacteria***
Staphylococcus aureus *Staphylococcus epidermidis* *Streptococcus pneumoniae*	*Enterobacter cloacae* *Haemophilus influenzae* *Proteus mirabilis* *Pseudomonas aeruginosa*

Corneal Ulcers

Gram-positive Bacteria	*Gram-negative Bacteria*
Staphylococcus aureus *Staphylococcus epidermidis* *Streptococcus pneumoniae*	*Pseudomonas aeruginosa* *Serratia marcascens** *Anaerobic Species* *Propionibacterium acnes*

**Efficacy for this organism was studied in fewer than 10 infections*

4.2 Posology and method of administration

The recommended dosage regimen for the treatment of bacterial conjunctivitis is as follows:

Days 1 and 2	Instill one to two drops every 2–4 hours in the affected eye(s).
Days 3 through 7	Instill one to two drops four times daily.

The recommended dosage regimen for the treatment of **bacterial corneal ulcer** is as follows:

Days 1 and 2	Instill one to two drops into the affected eye every 30 minutes, while awake. Awaken at approximately 4 and 6 hours after retiring and instill one to two drops.
Days 3 through 7 to 9	Instill one to two drops hourly, while awake.
Days 7 to 9 through treatment completion	Instill one to two drops, four times daily.

The length of treatment should not exceed 10 days.

4.3 Contraindications

The use of Ofloxacin Eye/Ear Drops is contraindicated in patients with hypersensitivity to ofloxacin, any of its excipients or any other quinolones.

4.4 Special warnings and precautions for use

Not For Injecvtion.

Ofloxacin Eye/Ear Drop**s** should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

There are rare reports of anaphylactic reaction/shock and fatal hypersensitivity reactions in patients receiving systemic quinolones, some following the first dose, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angio-oedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching. A rare occurrence of Stevens-Johnson syndrome, which progressed to toxic epidermal necrolysis, has been reported in a patient who was receiving topical ophthalmic ofloxacin. If an allergic reaction to ofloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy and, where appropriate, fluorescein staining. Ofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

The systemic administration of quinolones, including ofloxacin, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Ofloxacin, administered systemically at 10 mg/kg/day in young dogs (equivalent to 110 times the maximum recommended daily adult ophthalmic dose) has been associated with these types of effects.

When using ofloxacin ophthalmic solution, the risk of rhinopharyngeal passage, which can contribute to the occurrence and the diffusion of bacterial resistance, should be considered.

If worsening infection occurs, or if clinical improvement is not noted within a reasonable period, discontinue use and institute alternative therapy.

Cardiac Disorders

Caution should be taken when using fluoroquinolones, including ofloxacin ophthalmic solution, in patients with known risk factors for prolongation of the QT interval such as the following:

- 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 ofloxacin ophthalmic solution, in these populations.

Data are very limited to establish efficacy and safety of ofloxacin ophthalmic 0.3% solution, in the treatment of conjunctivitis in neonates.

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

Geriatric Patients

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

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 (NSAIDs). 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.

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 6 months in animal studies, including studies in monkeys.

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

Ofloxacin Eye/Ear Drops contain the preservative benzalkonium chloride which may cause ocular irritation and discolour soft contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Ofloxacin was not mutagenic in the Ames test, *in vitro* and *in vivo* cytogenic assay, sister chromatid exchange assay (Chinese hamster and human cell lines), unscheduled DMA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocyte, and in the mouse lymphoma assay.

In fertility studies in rats, ofloxacin did not affect male or female fertility or morphological or reproductive performance at oral dosing up to 360 mg/kg/day (equivalent to 4,000 times the maximum recommended daily ophthalmic dose).

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with Ofloxacin Eye/Ear Drops. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

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 NSAIDs, this has not been reported with the concomitant systemic use of NSAIDs and ofloxacin.

Ofloxacin ophthalmic solution, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval.

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 Ofloxacin 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, Ofloxacin 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. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

Ophthalmic Use

The most frequently reported drug-related adverse reaction was transient ocular burning or discomfort. Other reported reactions include stinging, redness, itching, chemical conjunctivitis/keratitis, ocular/periocular/facial oedema, foreign-body sensation, photophobia, blurred vision, tearing, dryness, and eye pain. Rare reports of dizziness and nausea have been received.

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 under the following frequency categories: 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); and not known (cannot be estimated from the available data):

Immune System Disorders
Not Known: hypersensitivity reactions, including signs or symptoms of eye allergy (such as eye pruritus and eyelid pruritus) and anaphylactic reactions (such as angio-oedema, dyspnoea, anaphylactic shock, oropharyngeal swelling, facial oedema and tongue swollen)
Nervous System Disorders
Not Known: dizziness
Eye Disorders
Common: eye irritation; ocular discomfort
Not Known: keratitis; conjunctivitis; vision blurred; photophobia; eye oedema; 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
Gastrointestinal Disorders
Not Known: nausea
Skin and Subcutaneous Tissue Disorders
Not Known: Stevens-Johnson syndrome; toxic epidermal necrolysis
Systemic absorption of fluoroquinolones has been reported to cause the adverse effects such as low blood sugar and mental health-related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health side effects that are more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below:

- Disturbances in attention
- Disorientation
- Agitation

- Nervousness
- Memory impairment
- Serious disturbances in mental abilities (delirium)

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

4.9 Overdose

An ocular overdose can be flushed from the eye(s) with lukewarm water. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. Pharmacological properties

Pharmacotherapeutic group: Ophthalmologicals, anti-infectives, fluoroquinolones
ATC code: S01AE01

5.1 Pharmacodynamic properties

Ofloxacin is a synthetic, fluorinated 4-quinolone antibacterial agent with activity against a broad spectrum of Gram-negative and, to a lesser degree, Gram-positive organisms. The primary mechanisms of action through inhibition of bacterial DNA gyrase, the enzyme responsible for maintaining the structure of DNA.

Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has been shown to be active against most strains of the following organisms, both *in vitro* and clinically:

Aerobic Gram-positive	***Aerobic Gram-negative***
Staphylococcus aureus	*Enterobacter cloacae*
Staphylococcus epidermidis	*Haemophilus influenzae*
Streptococcus pneumoniae	

Anaerobic Species	*Proteus mirabilis*
Propionibacterium acnes	*Pseudomonas aeruginosa*
	*Serratia marcescens**

*Efficacy for this organism was studied in fewer than ten infections.

The safety and effectiveness of ofloxacin ophthalmic solution in treating ophthalmologic infections due to the following organisms have not been established in adequate and well-controlled clinical trials. Ofloxacin ophthalmic solution has been shown to be active *in vitro* against most strains of these organisms but the clinical significance in ophthalmologic infections is unknown.

Aerobes, Gram-positive	
Enterococcus faecalis	*Staphylococcus hominus*
Listeria monocytogenes	*Staphylococcus simulans*
Staphylococcus capitis	*Streptococcus pyogenes*
Aerobes, Gram-negative	
Acinetobacter calcoaceticus var. anitratus	*Klebsiella pneumoniae*
Acinetobacter calcoaceticus var. lwoffii	*Moraxella (Branhamella) catarrhalis*
Citrobacter diversus	*Moraxella lacunata*
Citrobacter freundii	*Morganella morganii*
Enterobacter aerogenes	*Neisseria gonorrhoeae*
Enterobacter agglomerans	*Pseudomonas acidovorans*
Escherichia coli	*Pseudomonas fluorescens*
Haemophilus parainfluenzae	*Shigella sonnei*
Klebsiella oxytoca	
Other	
Chlamydia trachomatis	

5.2 Pharmacokinetic Properties

After ophthalmic instillation, ofloxacin is well maintained in the tear film.

In a healthy volunteer study, mean tear film concentrations of ofloxacin measured 4 hours after topical dosing (9.2 µg/g) were higher than the 2 µg/ml minimum concentration of ofloxacin necessary to inhibit 90% of most ocular bacterial strains (MIC_{90}) *in vitro*.

Maximum serum ofloxacin concentrations after 10 days of topical dosing were about 1,000 times lower than those reported after standard oral doses of ofloxacin, and no systemic side effects attributable to topical ofloxacin were observed.

Serum, urine and tear concentrations of ofloxacin were measured in 30 healthy women at various time points during a 10-day course of treatment with ofloxacin ophthalmic solution. 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 (day 1) to 1.9 ng/mL (day 11) after QID dosing for 10½ days. Maximum serum ofloxacin concentrations after 10 days of topical ophthalmic dosing were more than 1,000 times lower than those reported after standard oral doses of ofloxacin.

Tear ofloxacin concentrations ranged from 5.7 to 31 mcg/g during the 40-minute period following the last dose on day 11. Mean tear concentration measured 4 hours after topical ophthalmic dosing was 9.2 mcg/g.

Corneal tissue concentrations of 4.4 mcg/mL were observed 4 hours after beginning topical ocular application of two drops of ofloxacin ophthalmic solution every 30 minutes. Ofloxacin was excreted in the urine primarily unmodified.

5.3 Preclinical safety data

Systemic toxicity studies have been conducted in a number of animal species at acute, subacute and chronic levels using a variety of experimental animals. The choices were consistent with general practices in a 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 Solution
Disodium Edetate
Sodium Chloride
Sodium Hydroxide
Hydroxypropyl Methyl Cellulose
Water for Injection

6.2 Incompatibilities

None Known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store Protected from light at a temperature not exceeding 30°C**.**

6.5 Nature and contents of container

10ml White HDPE vial packed in a Carton along with Insert.

6.6 Special precautions for disposal and other handling

None Known.

7. Manufactured By

Scott-Edil Pharmacia Limited,
56, EPIP, Phase-I, Jharmajri,
Baddi, Distt. Solan- 173205 (H.P)
INDIA

8. Marketed By

Simpec Pharmaceutical Ltd.
No. 2 Ajaegbue Street-Fegge Onitsha
Anambra State, Nigeria

9. Date of revision of the text

August 2022

10. DOSIMETRY (IF APPLICABLE)

Not applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable