For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

OFLOXIBACT EYE DROPS

1. Generic Name

Ofloxacin Ophthalmic Solution I.P.

2. Qualitative and quantitative Composition:

Ofloxacin I.P. …… 0.3% w/v

Preservative:

Benzalkonium

Chloride Solution I.P. …… 0.02% w/v

Aqueous Vehicle …… q.s.

The List of Excipients used are Sodium Chloride, Sodium Acetate Anhydrous, Sodium Hydroxide Pellets, Benzalkonium Chloride Solution, Hydroxy Propyl Methyl Cellulose, Sodium Metabisulphite and Di Sodium Edetate.

3. Dosage form and strength

Dosage form: Drops

Strength: 0.3% w/v

4. Clinical particulars

4.1. Therapeutic indication

For the topical treatment of external infection of eyes in adults & children above 1 year.

4.2. Posology and method of administration

The recommended dosage regimen for the treatment of bacterial conjunctivitis	
Days 1 and 2	Instill one to two drops every two to four 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 ulcers	
Days 1 and 2	Instill one to two drops into the affect ed eye every 30 minutes, while awake. Awaken at approximately four and six 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.

4.3. Contraindications

- Ofloxacin ophthalmic solution is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

4.4. Special warnings and precautions for use

WARNINGS

NOT FOR INJECTION

Ofloxacin ophthalmic solution should not be injected subconjunctival, 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, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, 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.

The drug may cause 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 more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:

- Disturbances in attention
- Disorientation
- Agitation
- Nervousness
- Memory impairment
- Serious disturbances in mental abilities called delirium

PRECAUTIONS

General

As with other anti-infectives, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs discontinue use and institute alternative therapy. Whenever clinical judgment 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.

Information for Patients

Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

4.5. Drugs interactions

Specific drug interaction studies have not been conducted with ofloxacin ophthalmic solution. 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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Teratogenic Effects

Ofloxacin has been shown to have an embryocidal effect in rats and in rabbits when given in doses of 810 mg/kg/day (equivalent to 9000 times the maximum recommended daily ophthalmic dose) and 160 mg/kg/day (equivalent to 1800 times the maximum recommended daily ophthalmic dose). These dosages 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. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Nonteratogenic Effects

Additional studies in rats with doses up to 360 mg/kg/day during late gestation showed no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn.

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

In nursing women, a single 200 mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical ophthalmic administration. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after oral administration; however, topical ocular administration of ofloxacin to immature animals has not shown any arthropathy. There is no evidence that the ophthalmic dosage form of ofloxacin has any effect on weight bearing joints.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

4.7. Effects on ability to drive and use machines

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Ofloxacin eye drop is known.

4.8. Undesirable effects

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 edema, foreign body sensation, photophobia, blurred vision, tearing, dryness, and eye pain. Rare reports of dizziness and nausea have been received.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

Human experience of overdose with Ofloxibact Eye Drops is limited.

5. Pharmacological properties

5.1. Mechanism of Action

Ofloxacin has in vitro activity against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria. Ofloxacin is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Ofloxacin is thought to exert a bactericidal effect on susceptible bacterial cells by inhibiting DNA gyrase, an essential bacterial enzyme that is a critical catalyst in the duplication, transcription, and repair of bacterial DNA.

5.2. Pharmacodynamic properties

Ofloxacin is a quinolone/fluoroquinolone antibiotic. Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria

Clinical Studies

Conjunctivitis

In a randomized, double-masked, multicentre clinical trial, ofloxacin ophthalmic solution was superior to its vehicle after 2 days of treatment in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated a clinical improvement rate of 86% (54/63) for the ofloxacin treated group versus 72% (48/67) for the placebo treated group after 2 days of therapy. Microbiological outcomes for the same clinical trial demonstrated an eradication rate for causative pathogens of 65% (41/63) for the ofloxacin treated group versus 25% (17/67) for the vehicle treated group after 2 days of therapy. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

Corneal Ulcers

In a randomized, double-masked, multi-centre clinical trial of 140 subjects with positive cultures, ofloxacin ophthalmic solution treated subjects had an overall clinical success rate (complete re-epithelialization and no progression of the infiltrate for two consecutive visits) of 82% (61/74) compared to 80% (53/66) for the fortified antibiotic group, consisting of 1.5% tobramycin and 10% cefazolin solutions. The median time to clinical success was 11 days for the ofloxacin treated group and 10 days for the fortified treatment group.

5.3. Pharmacokinetic properties

Serum, urine and tear concentrations of ofloxacin were measured in 30 healthy women at various time points during a ten-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 on day one to 1.9 ng/mL on day 11 after QID dosing for 10 1/2 days. Maximum serum ofloxacin concentrations after ten days of topical ophthalmic dosing were more than 1000 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 four hours after topical ophthalmic dosing was 9.2 mcg/g.

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

Microbiology

Ofloxacin has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria. Ofloxacin is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Ofloxacin is thought to exert a bactericidal effect on susceptible bacterial cells by inhibiting DNA gyrase, an essential bacterial enzyme which is a critical catalyst in the duplication, transcription, and repair of bacterial 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, in conjunctival and/or corneal ulcer infections

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

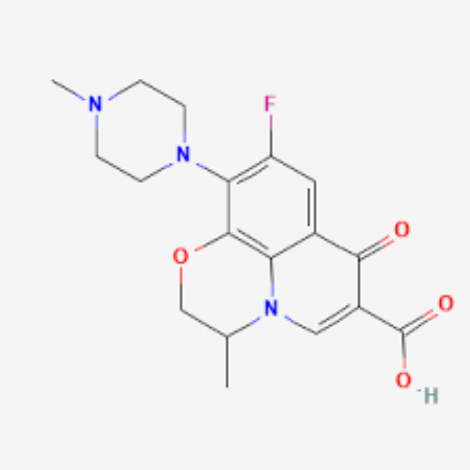
Ofloxacin was not mutagenic in the Ames test, in vitroand in vivo cytogenic assay, sister chromatid exchange assay (Chinese hamster and human cell lines), unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or mouse micronucleus assay. Ofloxacin was positive in the 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 4000 times the maximum recommended daily ophthalmic dose).

7. Description

Ofloxacin

Ofloxacin is (RS)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7H-pyridol[1,2,3-de]-1,4-benzoxazine-6-carboxyllic acid. The empirical formula is $C_{18}H_{20}FN_3O_4$ and its molecular weight is 361.4 g/mol. The chemical structure of Ofloxacin is:



Ofloxibact

Ofloxacin Ophthalmic Solution is Light Yellow colour, clear liquid.

The List of Excipients used are Sodium Chloride, Sodium Acetate Anhydrous, Sodium Hydroxide, Benzalkonium Chloride Solution, Hydroxy Propyl Methyl Cellulose, Sodium Metabisulphite and Di Sodium Edetate.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

Ofloxibact is available in a pack of 15 ml vial.

8.4. Storage and handing instructions

Store at a temperature not exceeding 30°C, Protected from light. Keep out of reach of children.

For Ophthalmic use only.

Shake well before use.

Not for Injection.

For external use only.

Replace the cap after every use.

Warnings:

1. If irritation persists or increases, discontinue the use and consult the physician.
2. Do not touch the vial tip to any surface since this may contaminate the solution.

Use the solution within one month after opening the container.

Caution:

This drug may cause low blood sugar and mental health related side effects.

9. **Patient Counselling Information**

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. **Details of manufacturer**

East African (India) Overseas
Plot No. 8, Pharmacity, Selaqui,
Dehradun, 248011, (U.K.)

11. **Details of permission or licence number with date**

Mfg. Lic. No. is 94/UA/SC/P-2009, issue on 11.04.2023.

12. **Date of revision**

NA

MARKETED BY

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