OFLOX D Eye Drops (Ofloxacin 0.3% + Dexamethasone sodium phosphate 0.1%)

Qualitative And Quantitative Composition

Each ml contains:
- Ofloxacin IP .....................................................................................................0.3% w/v
- Dexamethasone Sodium Phosphate IP equivalent to Dexamethasone ...........0.1% w/v
- Benzalkonium Chloride IP ............................................................................0.01% w/v  (as Preservative)
- Sterile aqueous vehicle ..................................................................................q.s.

Dosage Form And Strength

Ofloxacin (0.3% w/v) and Dexamethasone (0.1% w/v) Eye Drops

Clinical Particulars

Therapeutic Indications

The ofloxacin-dexamethasone combination is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial ocular infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and selected infectious conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical radiation, or thermal burns, or penetration of foreign bodies.

Posology and Method of Administration

One or two drops of OFLOX-D Eye Drops instilled into the conjunctival sacs every 2 to 4 hours for the first 2 days and then four times daily. The length of treatment should not exceed 10 days.

Contraindications

The use of OFLOX-D Eye Drops is contraindicated in patients with hypersensitivity to ofloxacin, to other quinolones, to dexamethasone, to other corticosteroid or any of the ingredient of the formulation.

The use of OFLOX-D Eye Drops is also contraindicated in epithelial herpes simplex keratitis (dendritic keratitis), acute infectious stages of vaccinia, varicella, and in other viral diseases of the conjunctiva and cornea, mycobacterial infection of the eye and fungal diseases of ocular structures.

Special Warnings and Precautions for Use
OFLOX-D Eye Drops should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

**Ofloxacin**

Safety and effectiveness in infants below the age of 1 year have not been established.

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 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 super-infection 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, the risk of rhinopharyngeal passage, which can contribute to the occurrence and the diffusion of bacterial resistance, should be considered.

**Cardiac Disorders**

Caution should be taken when using fluoroquinolones, including ofloxacin, 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) elderly
- 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, in these populations.

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 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.

Dexamethasone Sodium Phosphate

**General**

The possibility of persistent fungal infections of the cornea should be considered after prolonged corticosteroid dosing. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Prolonged use may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Prolonged use may suppress the host response and, thus, increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. In acute purulent conditions of the eye or ear, corticosteroids may mask infection or enhance existing infection. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients.

Employment of corticosteroid medication in the treatment of herpes simplex other than epithelial herpes simplex keratitis, in which it is contraindicated, requires great caution; periodic slit-lamp microscopy is essential.

Care should be taken to ensure that the eye is not infected before dexamethasone eye drops are used. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. Caution is also necessary when used in conjunction with antiviral therapy in the treatment of stromal keratitis or uveitis and use of periodic slit-lamp microscopy.

Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral and fungal infections and mask the clinical signs of infections, preventing recognition of ineffectiveness of the antibiotic. In such cases, antibiotic therapy is mandatory. Fungal infection should be suspected in patients with persistent corneal ulceration who have been or are receiving these drugs, and corticosteroid therapy should be discontinued if fungal infection occurs.

This medicinal product contains phosphates, which may lead to corneal deposits or corneal opacity when topically administered. It should be used with caution in patients presenting with compromised cornea and in instances where the patient is receiving polypharmacy with other phosphate-containing eye medications.

Topical corticosteroids should not be used for longer than 1 week except under ophthalmic supervision. Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity, visual field defects and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure and the lens should be checked routinely and frequently, particularly in patients with a history or presence of glaucoma. The dose of anti-glaucoma medication may need to be adjusted in these patients. Prolonged use may also increase the hazard of secondary ocular infections. Topical ophthalmic corticosteroids may slow corneal wound healing.

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ophthalmic dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, treatment should be progressively...
Contact lenses should not be worn during treatment with corticosteroid eye drops due to increased risk of infection. Systemic absorption may be reduced by compressing the lacrimal sac at the medial canthus for a minute during and following the instillation of the drops. (This blocks the passage of drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa. It is especially advisable in children.)

**Paediatric Patients**
In children, long-term, continuous corticosteroid therapy should be avoided due to possible adrenal suppression.

OFLOX-D Eye Drops contain the preservative benzalkonium chloride, which may cause ocular irritation and discolour soft contact lenses.

**Drug Interactions**

**Ofloxacin**
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.

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 central nervous system (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.

**Dexamethasone Sodium Phosphate**
The risk of increased intraocular pressure associated with prolonged corticosteroid therapy may be more likely to occur with concomitant use of anticholinergics, especially atropine and related compounds, in patients predisposed to acute-angle closure.

The risk of corneal deposits or corneal opacity may be more likely to occur in patients presenting with compromised cornea and receiving polypharmacy with other phosphate-containing eye medications.

The following drug interactions are possible, but are unlikely to be of clinical significance, following the use of dexamethasone ophthalmic solution, 1%, in the eye(s):

- The therapeutic efficacy of dexamethasone may be reduced by phenytoin, phenobarbitone, ephedrine and rifampicin.
- Glucocorticoids may increase the need for salicylates as plasma salicylate clearance is increased.
- CYP3A4 inhibitors (including ritonavir and cobicistat) may decrease dexamethasone clearance, resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid effects.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

**Use in Special Populations**

**Pregnancy Category C Drug**

**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 9,000 times the maximum recommended daily ophthalmic dose) and 160 mg/kg/day (equivalent to 1,800 times the maximum recommended daily ophthalmic dose). These dosages resulted in decreased foetal body weight and increased foetal mortality in rats and rabbits, respectively. Minor foetal 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.

There are no adequate and well-controlled studies in pregnant women. OFLOX-D Eye Drops should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the embryo or foetus.

Non-Teratogenic Effects
Additional studies in rats with doses up to 360 mg/kg/day during late gestation showed no adverse effect on late foetal development, labour, 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 foetus.

Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the therapeutic dose.

In the mouse, corticosteroids produce foetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced foetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc.

There are no adequate or well-controlled studies in pregnant women. Studies in animals have shown that topically applied steroids can be absorbed systemically and can cause abnormalities of foetal development in pregnant animals. Although the relevance of these findings to human beings has not been established, dexamethasone sodium phosphate ophthalmic solution should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the embryo or foetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Lactating Women
In nursing women, a single 200 mg oral dose resulted in concentrations of ofloxacin in milk that were like those found in plasma.

Because ofloxacin and other quinolones taken systemically are excreted in breast milk, there is potential for harm to nursing infants. Similarly, systemically administered corticosteroids appear in human milk in quantities that could affect the child being breastfed. However, when instilled topically, systemic exposure is low.

It is not known whether ofloxacin and dexamethasone solution is excreted in human milk following topical administration. Because of the potential for serious adverse reactions from ofloxacin or dexamethasone 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.

Paediatric Patients
Safety and effectiveness of ofloxacin in infants below the age of 1 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.

Safety and effectiveness of dexamethasone in paediatric patients have not been established.

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

Effects on Ability to Drive and Use Machines
As with any topical ophthalmic medicinal product, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.
Undesirable Effects

**Ofloxacin**

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 toastes 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 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-related 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)

**Dexamethasone Sodium Phosphate**

Glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens, including herpes simplex, and perforation of the globe have been reported.

Rarely, filtering blebs have been reported when topical steroids have been used following cataract surgery. Rarely, stinging or burning may occur.
The following undesirable effects are classified according to 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 <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

**Endocrine Disorders**

*NOT KNOWN (cannot be estimated from the available data)*: Cushing's syndrome, adrenal suppression

**Ocular Disorders**

*VERY COMMON (>1/10)*: intraocular pressure increased (after 2 weeks of treatment).

*COMMON (>1/100, <1/10)*: ocular discomfort after instillation, irritation, burning, eye pruritus and blurred vision. These symptoms are mild and transient with no consequences.

*UNCOMMON (>1/1,000, <1/100)*: signs and symptoms of allergic or hypersensitive reactions can occur. The following corticoid-specific undesirable effects can occur: delay in healing, risk of posterior subcapsular cataract formation, opportunist infections and glaucoma.

*VERY RARE (<1/10,000, including isolated reports)*: conjunctivitis, eyelid oedema, corticoid-induced uveitis, keratitis, corneal thinning, corneal oedema and ulcerations. Cases of corneal calcification have been reported in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas. Due to the steroid component, in diseases causing thinning of the cornea or sclera, there is a higher risk for perforation especially after topical long treatments.

**General Disorders and Administration Site Conditions**

*UNCOMMON (>1/1,000, <1/100)*: after long treatment, systemic absorption can occur with an inhibition of the adrenal function.

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.

### 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.

### Pharmacological Properties

#### Mechanism of Action

Ofloxacin has *in vitro* activity against a broad range of Gram-positive and Gram-negative aerobic and anaerobic bacteria. It 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.

Dexamethasone sodium phosphate, a corticosteroid, suppresses the inflammatory response to a variety of agents. Since they may inhibit the body's defence mechanism against infection, a concomitant antimicrobial drug may be necessary when this inhibition is clinically significant.

#### Pharmacodynamic Properties

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

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 is 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:

<table>
<thead>
<tr>
<th>Aerobes, Gram-positive</th>
<th>Aerobes, Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Enterobacter cloacae</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Proteus mirabilis</td>
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<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><strong>Anaerobic Species</strong></td>
<td><strong>Serratia marcescens</strong></td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
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</table>

*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.

<table>
<thead>
<tr>
<th>Aerobes, Gram-positive</th>
<th>Aerobes, Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td><em>Enterococcus hominus</em></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Staphylococcus simulans</td>
</tr>
<tr>
<td>Staphylococcus capitis</td>
<td><em>Streptococcus pyogenes</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aerobes, Gram-negative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter calcoaceticus var. anitratus</td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td>Acinetobacter calcoaceticus var. lwoffii</td>
<td>Moraxella (Branhamella) catarrhalis</td>
</tr>
<tr>
<td>Citrobacter diversus</td>
<td>Moraxella lacunata</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>Morganella morganii</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Enterobacter agglomerans</td>
<td>Pseudomonas acidovorans</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Pseudomonas fluorescens</td>
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<tr>
<td><em>Haemophilus parainfluenza</em></td>
<td>Shigella sonnei</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
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</tbody>
</table>

*Other

Chlamydia trachomatis

Clinical Studies

Conjunctivitis

In a randomised, 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 randomised, double-masked, multicentre clinical trial of 140 subjects with positive cultures, ofloxacin ophthalmic solution-treated subjects had an overall clinical success rate (complete re-epithelialisation and no progression of the infiltrate for two consecutive visits) of 82% (61/74) compared with 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. 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.

**Dexamethasone Sodium Phosphate**

Pharmacotherapeutic group: Corticosteroids, plain, ATC code: S01 BA01

Dexamethasone is a highly potent and long-acting glucocorticoid. It has an approximately 7 times greater anti-inflammatory potency than prednisolone, another commonly prescribed corticosteroid.

The actions of corticosteroids are mediated by the binding of the corticosteroid molecules to receptor molecules located within sensitive cells. Corticosteroid receptors are present in human trabecular meshwork cells and in rabbit iris ciliary body tissue.

Corticosteroids will inhibit phospholipase A2, thereby preventing the generation of substances that mediate inflammation, e.g. prostaglandins. Corticosteroids also produce a marked, though transient, lymphocytopenia. This depletion is due to redistribution of the cells, the T-lymphocytes being affected to a greater degree than the B-lymphocytes. Lymphokine production is reduced, as is the sensitivity of macrophages to activation by lymphokines. Corticosteroids also retard epithelial regeneration, diminish post-inflammatory neovascularisation and reduce towards normal levels the excessive permeability of inflamed capillaries. The actions of corticosteroids described above are exhibited by dexamethasone sodium phosphate and they all contribute to its anti-inflammatory effect.

**Pharmacokinetic Properties**

**Ofloxacin**

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\textsubscript{90} \textit{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.
**Dexamethasone Sodium Phosphate**

**Absorption**
When given topically to the eye, dexamethasone is absorbed into the aqueous humour, cornea, iris, choroid, ciliary body and retina. Systemic absorption occurs but may be significant only at higher dosages or in extended paediatric therapy. Up to 90% of dexamethasone is absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide individual variations.

**Distribution**
Tissue distribution studies in animals show a high uptake of dexamethasone sodium phosphate by the liver, kidneys and adrenal glands; a volume of distribution has been quoted as 0.58 l/kg. In humans, over 60% of circulating steroids are excreted in the urine within 24 hours, largely as unconjugated steroid.

**Biotransformation**
Dexamethasone sodium phosphate is rapidly converted to dexamethasone within the circulation. Up to 77% of dexamethasone is bound to plasma proteins, mainly albumin. This percentage, unlike cortisol, remains practically unchanged with increasing steroid concentrations. The mean plasma half-life of dexamethasone is 3.6 ± 0.9 hours.

**Elimination**
Dexamethasone also appears to be cleared more rapidly from the circulation of the foetus and neonate than in the mother; plasma dexamethasone levels in the foetus and the mother have been found in the ratio of 0.32:1.

### Non-Clinical Properties

#### Animal Toxicology or Pharmacology

**Ofloxacin**
There are no toxicological safety issues with this product in humans as the level of systemic absorption from topical ocular administration of ofloxacin is minimal.

Animal studies in the dog have found cases of arthropathy in weight-bearing joints of juvenile animals after high oral doses of certain quinolones. However, these findings have not been seen in clinical studies and their relevance to humans is unknown.

**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 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 4,000 times the maximum recommended daily ophthalmic dose).

**Dexamethasone Sodium Phosphate**
Repeat-dose topical ocular safety studies with dexamethasone in rabbits have shown systemic corticosteroid effects. Such effects are considered to be unlikely when dexamethasone eye drops are used as recommended.

Dexamethasone was clastogenic in the *in vitro* human lymphocyte assay and *in vivo* in the mouse micronucleus assay at doses in excess of those obtained following topical application. Conventional carcinogenicity studies with dexamethasone have not been performed.

Dexamethasone has been found to be teratogenic in animal models. Dexamethasone induced abnormalities of foetal development, including cleft palate, intra-uterine growth retardation and effects on brain growth and development.
Description

OFLOX-D Eye Drops are a combination of ofloxacin, a fluoroquinolone antimicrobial, and dexamethasone, a potent corticosteroid.

Pharmaceutical Particulars

- **Incompatibilities**
  Not known

- **Shelf-Life**
  As on the pack.

Packaging Information

OFLOX-D Eye Drops: Vial of 10 ml

Storage and Handling Instructions

Store in cool, dark place

Patient Counselling Information

**What is OFLOX-D Eye Drops?**

OFLOX-D Eye Drops are a combination of ofloxacin, a fluoroquinolone antimicrobial, and dexamethasone, a potent corticosteroid.

- Do not use if you have an allergy to this drug
- Do not use if you are allergic (hypersensitive) to ofloxacin, benzalkonium chloride, dexamethasone sodium phosphate, any of the other ingredients, or any other quinolones.
- Before you use this drug, tell your HCP about other medication.

Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines, including medicines obtained without prescription.

Tell your doctor if you are using ritonovir or cobicistat as this may increase the amount of dexamethasone in the blood.

You must tell your doctor if you are taking other medicines that can alter your heart rhythm such as medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), tricyclic antidepressants, some antimicrobials (that belong to the group of macrolides), and/or some antipsychotics.

**How should I use OFLOX-D Eye Drops?**

Always use OFLOX-D Eye Drops exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**What are the possible side effects?**

Like all medicines, OFLOX-D Eye Drops can cause side effects, but not everyone gets them. Occasionally, this medicine may cause temporary stinging, burning, redness or watering of the eyes.

**Serious side effects**

If you have one or more of the following side effects, you may have had a serious allergic reaction. Stop using OFLOX-D Eye Drops immediately and contact your physician.

**Allergic reactions**
Allergic reactions in the eye (including itchiness of the eye and/or eyelid)
Inflammation of the skin due to allergy (including: rash, itching or hives)
Severe sudden life-threatening allergic reaction (anaphylactic) presenting as swelling beneath the skin that can occur in areas such as the face, lips or other parts of the body, swelling of the mouth, tongue or throat that can obstruct the airways (which may cause wheezing, difficulty swallowing, breathing or shortness of breath)
Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of OFLOX-D Eye Drops, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk.

Other side effects
The following side effects are also known to occur. You should see your doctor if any of the following side effects prove troublesome or if they are long-lasting.
Common side effects (may affect up to 1 in 10 people)
Eye irritation
Ocular discomfort
In very rare cases, cloudy patches may develop on the cornea due to calcium build-up during treatment.
Frequency not known (cannot be estimated from available data)

Side effects affecting the eye:
Visual disturbance
Tearing
Inflammation
Redness
Sensitivity to light
A feeling that something is in your eye
Eye swelling
Swelling around the eyes (including eyelid swelling)
Eye pain
Dryness (mild stinging or burning)

Side effects affecting the body:
Dizziness
Nausea

Side effects affecting the heart:
Abnormal fast heart rhythm
Life-threatening irregular heart rhythm
Alteration of the heart rhythm (called ‘prolongation of QT interval’, seen on ECG electrical activity of the heart)

How should I store OFLOX-D Eye Drops?
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date stated on pack

General information about safe and effective use of this drug
OFLOX-D Eye Drops are a combination of ofloxacin, a fluoroquinolone Antimicrobial, and dexamethasone, a potent corticosteroid. It is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial ocular infection or a risk of bacterial ocular infection exists.
This product should be used with caution in patients sensitive to other quinolone antibacterial agents.
This product should be used with caution in patients with a defect or ulceration of the surface of the eye.

**Heart problems**: Caution should be taken when using this kind of medicine, if you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called ‘bradycardia’), have a weak heart (heart failure), have a history of heart attack (myocardial infarction), you are female or elderly or you are taking other medicines that result in abnormal ECG changes.

Tell your doctor before you start using OFLOX-D Eye Drops if you are pregnant or if you are breastfeeding. Your doctor can then decide whether you can use OFLOX-D Eye Drops.

What are the ingredients?
The active substances are ofloxacin (0.3% w/v) and dexamethasone sodium phosphate (0.1% w/v). The other ingredients are benzalkonium chloride (0.01% w/v) and purified water.

Any other information
Avoid contaminating the applicator tip with material from the eye(s), fingers or other source. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

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.

The preservative in OFLOX-D Eye Drops, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling OFLOX-D Eye Drops before they insert their lenses.

### Details Of The Manufacturer

M/s. Cipla Ltd,
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### Details Of Permission Or Licence Number With Date

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### OFLOX D Eye Drops

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