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

Composition

Each ml contains:
- Ofloxacin USP ................................0.3% w/v
- Dexamethasone sodium phosphate IP .... 0.1% w/v
  (Equivalent to Dexamethasone)
- Benzalkonium Chloride NF ............... 0.01% w/v
- Sterile aqueous vehicle .................... q.s

Dosage Form

Solution

Pharmacology

Pharmacodynamics

Ofloxacin
Ofloxacin has \textit{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 \textit{in vitro} and clinically, in conjunctival and/or corneal ulcer infections.

Gram-Positive Aerobes
- \textit{Staphylococcus aureus}
- \textit{Staphylococcus epidermidis}
- \textit{Streptococcus pneumoniae}
Anaerobic Species
*Propionibacterium acnes*

Gram-Negative Aerobes
*Enterobacter cloacae*
*Haemophilus influenzae*
*Proteus mirabilis*
*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.

Gram-positive Aerobes
*Enterococcus faecalis*
*Listeria monocytogenes*
*Staphylococcus capitis*
*Staphylococcus hominus*
*Staphylococcus simulans*
*Streptococcus pyogenes*

Gram-negative Aerobes
*Acinetobacter calcoaceticus var. anitratus*
*Acinetobacter calcoaceticus var. lwoffii*
*Citrobacter diversus*
*Citrobacter freundii*
*Enterobacter aerogenes*
*Enterobacter agglomerans*
*Escherichia coli*
*Haemophilus parainfluenzae*
*Klebsiella oxytoca*
*Klebsiella pneumoniae*
*Moraxella (Branhamella) catarrhalis*
*Moraxella lacunata*
*Morganella morganii*
*Neisseria gonorrhoeae*
*Pseudomonas acidovorans*
*Pseudomonas fluorescens*
*Shigella sonnei*

Other
*Chlamydia trachomatis*
Clinical Studies

Conjunctivitis

In a randomized, double-masked, multi-centre 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 treated with 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.

Dexamethasone Sodium Phosphate

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

Dexamethasone sodium phosphate suppresses the inflammatory response to a variety of agents and it probably delays or slows healing. No generally accepted explanation of these steroid properties has been advanced.

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 which mediate inflammation, for example, 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 neo-vascularisation and reduce towards normal levels the excessive permeability of inflamed capillaries.

The actions of corticosteroids described above are exhibited by dexamethasone sodium phosphate 0.1% and they all contribute to its anti-inflammatory effect.

Pharmacokinetics

Ofloxacin

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
0.4ng/mL to 1.9ng/mL. Maximum ofloxacin concentration increased from 1.1ng/mL on day one to 1.9ng/mL on day 11 after q.i.d dosing for 10 and a half days. Maximum serum ofloxacin concentrations after 10 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 mcg/g 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 4.4 mcg/mL was 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
Dexamethasone is absorbed rapidly after oral administration with a half-life of about 190 minutes. Sufficient absorption may occur after topical application to the skin and eye to produce systemic effects. In plasma dexamethasone protein binding is less than for most other corticosteroids. Corticosteroids diffuse into tissue fluids and cerebrospinal fluid but transplacental diffusion in significant amounts has not been demonstrated. Corticosteroids are metabolised in the liver the kidney and excrete in the urine. Metabolism is similar to other corticosteroids. Intraocular penetration occurs in significant amounts and contributes to the effectiveness of dexamethasone in anterior segment inflammatory disease.

When given topically to the eye, dexamethasone is absorbed into the aqueous humor, cornea, iris, choroid, ciliary body and retina. Systemic absorption occurs but may be significant only at higher dosages or in extended pediatric therapy.

Indications
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, selected infective conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical radiation, or thermal burns, or penetration of foreign bodies.

Dosage And Administration
One or two drops of OFLOX-D ophthalmic solution instilled into the conjunctival sacs every 4 to 6 hours.

Warnings And Precautions

General
Ofloxacin
Ofloxacin ophthalmic solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

Serious and occasionally, fatal hypersensitivity (anaphylactic) 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, 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 of 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.

When using 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, including fungi. If super-infection 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.

Caution should be taken when using fluoroquinolones, including ofloxacin 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)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Use ofloxacin with caution in patients who have exhibited sensitivities to other quinolone antibacterial agents.

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. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

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.

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.

Dexamethasone Sodium Phosphate
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 sub-capsular 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.

The possibility of persistent fungal infections of the cornea should be considered after prolonged corticosteroid dosing.

Contact lens wear is not recommended during treatment of an ocular inflammation.

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.

OFLOX- D ophthalmic drops contain the preservative benzalkonium chloride which may cause ocular irritation and discolour soft contact lenses.

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

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

Effect 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.
Drug Interactions

Specific drug interaction studies have not been conducted with ofloxacin and dexamethasone.

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.

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.

Ofloxacin, 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).

Pregnancy

Pregnancy Category C

Teratogenic Effects

There are no adequate and well-controlled studies in pregnant women. OFLOX-D 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 hypo-adrenalism.

Lactation

It is not known whether Ofloxacin and Dexamethasone solution is excreted in human milk following topical administration.

Because many drugs are excreted in human milk, caution should be exercised when OFLOX-D ophthalmic solution is administered to a nursing woman.

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 Use

Ofloxacin

Safety and effectiveness 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.

Dexamethasone Sodium Phosphate
Safety and effectiveness in paediatric patients have not been established.

### Geriatric Use

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

### 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.

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**

Very Rare: Hypersensitivity* (including angioedema, dyspnea, anaphylactic reaction/shock, oropharyngeal swelling and tongue swollen.

* Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin.

**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; Hypersensitivity (including Eye pruritus and Eyelid pruritus).

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: Periorbital oedema

Dexamethasone Sodium Phosphate

Glaucoma with optic nerve damage, visual acuity and field defects, posterior, cataract formation, secondary ocular infection from pathogens following suppression of host response, and perforation of the globe may occur.

Rarely, filtering blebs have been reported when topical steroids have been used following cataract surgery.

Rarely, stinging or burning may occur.

In clinical trials, the most common adverse reaction was ocular discomfort. The following adverse reactions 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 <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reaction are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience with dexamethasone sodium phosphate 0.1%:

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>MedDRA Preferred Term (v. 12.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known: hypersensitivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon: dysgeusia</td>
</tr>
<tr>
<td></td>
<td>Not known: dizziness, headache</td>
</tr>
</tbody>
</table>
Eye disorders

<table>
<thead>
<tr>
<th>Common: ocular discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: keratitis, conjunctivitis, keratoconjunctivitis sicca, corneal staining, photophobia, vision blurred, eyepruritus, foreign body sensation in eyes, lacrimation increased, abnormal sensation in eyes, eyelid margin crusting, eye irritation, ocular hyperaemia</td>
</tr>
<tr>
<td>Not known: intraocular pressure increased, visual acuity reduced, corneal erosion, eyelid ptosis, eye pain, mydriasis</td>
</tr>
</tbody>
</table>

Overdosage

An ocular overdose can be flushed from the eye(s) with lukewarm water.

Incompatibility

None known

Packaging Information

OFLOX-D Eye Drops:.............. Vial of 10 ml

Information For Patients

Avoid contaminating the applicator tip with material from the eye, 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 ophthalmic solution, 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 ophthalmic solution before they insert their lenses.

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OFLOX D Eye Drops

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