Oxop®-D Eye Drops

1. Generic Names

Ofloxacin

Dexamethasone

2. Composition

Each ml of Oxop eye drops contains:

Ofloxacin	0.3% w/v
Dexamethasone	0.1% w/v

3. Dosage form and strength

Topical ophthalmic solution containing Ofloxacin 0.3%(0.3mg/100ml).

4. Clinical particulars

4.1 Therapeutic indication

Oxop-D eye drops are indicated in:

- Bacterial Conjunctivitis
- Keratitis
- Post cataract surgery

4.2 Posology and method of administration

As directed by physician.

4.3 Contraindication

The use of Oxop-D eye drop (Ofloxacin) is contraindicated in patients with hypersensitivity to Ofloxacin or to other quinolones or to any of the components of the medication.

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

4.4 Special warnings and precautions for use

The prolonged use of antibiotics may occasionally result in overgrowth of non-susceptible organisms, including fungi. If new infections appear, the drug should be discontinued and appropriate measures instituted.

In all serious infections the topical use of Oxop eye drop (Ofloxacin) should be supplemented by appropriate systemic medication.

4.5 Drug interactions

- Ofloxacin

None are reported.

- Dexamethasone

The risk of increased intraocular pressure associated with prolonged corticosteroid therapy may be more likely to occur with concomitant use of anti-cholinergic, 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: 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. 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.

4.6 Use in special population

- Paediatric: Safety and effectiveness in infants below the age of one year have not been established.
- Geriatric: No overall clinical differences in safety or effectiveness have been observed between elderly and younger patients.
- Liver impairment: No data found.
- Renal failure: No data found.
- Pregnancy and lactation: There are no adequate and well-controlled studies in pregnant women. Oxop-D eye drop (Ofloxacin) should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

Adverse effects have occurred with steroid/anti-infective combination drugs, which can be attributed to the steroid component, the anti-infective component, or the combination. The most frequently reported drug-related adverse reactions seen with Ofloxacin are: transient ocular burning or discomfort. Other reported reactions include stinging, redness, itching, conjunctivitis/keratitis, periocular/facial edema, foreign body sensation, photophobia, blurred vision, tearing, dryness, and eye pain. The reactions due to the steroid component are: elevation of intraocular pressure with possible development of glaucoma, and infrequent optic nerve damage, posterior subcapsular cataract formation and delayed wound healing.

4.9 Overdose

There is limited experience of overdose with Oxop-D eye drop. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

- Ofloxacin

Oxop eye drop (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.

- Dexamethasone

Dexamethasone is a highly potent and long-acting glucocorticoid. The actions of corticosteroids are mediated by the binding of the corticosteroid molecules to receptor molecules located within sensitive cells. Corticosteroids will inhibit phospholipase A2 thereby preventing the generation of substances which mediate inflammation, for example, prostaglandins. Corticosteroids also produce a marked, though transient, lymphocytopaenia. 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 and they all contribute to its anti-inflammatory effect.

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.

Dexamethasone and its derivatives, dexamethasone sodium phosphate and dexamethasone acetate, are synthetic glucocorticoids. Used for its anti-inflammatory or immunosuppressive properties and ability to penetrate the CNS, dexamethasone is used alone to manage cerebral edema and with tobramycin to treat corticosteroid-responsive inflammatory ocular conditions.

5.3 Pharmacokinetic properties

- Ofloxacin

Findings of Serum, urine and tear concentrations of Ofloxacin: (10-day course)

The mean serum Ofloxacin concentration ranged from 0.4 ng/m to 1.9 ng/mL.

Tear Ofloxacin concentrations ranged from 5.7 to 31 mcg/g during the 40-minute period. Mean tear concentration measured 4 hours after topical ophthalmic dosing - 9.2 mcg/g.

Corneal tissue concentrations- 4.4 mcg/mL 4 hours after topical ophthalmic dosing Ofloxacin was excreted in the urine primarily unmodified.

- Dexamethasone

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 by the liver, kidney and adrenal glands; a volume of distribution has been quoted as 0.58 l/kg. In man, over 60% of circulating steroids are excreted in the urine within 24 hours, largely as unconjugated steroid.

Metabolism

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 ± 0.9h.

Distribution

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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Ofloxacin

Ocular toxicity and systemic adverse effects of 0.3% ofloxacin ophthalmic solution (0.3% ofloxacin) which was administered 3 times daily for one year were studied in dogs.

In general conditions, food intake, behavior and body weights, no significant difference was observed between the non treated group and 0.3% ofloxacin treated group throughout the experimental period. Signs for ocular toxicity such as anterior ocular irritation, abnormality of cornea and lens opacity, as well as fundus abnormality were no observed during ophthalmological examination in either group. Electroretinogram showed no abnormality by administration of 0.3% ofloxacin. Hematological examinations and blood chemistry resulted in normal values in any test item. Autopsy, organ weight, histopathology of ocular tissues and systemic organs showed no change due to ofloxacin.It is concluded from these results

that one year application of 0.3% ofloxacin ophthalmic solution to dogs causes neither ocular toxicity nor systemic adverse effect.

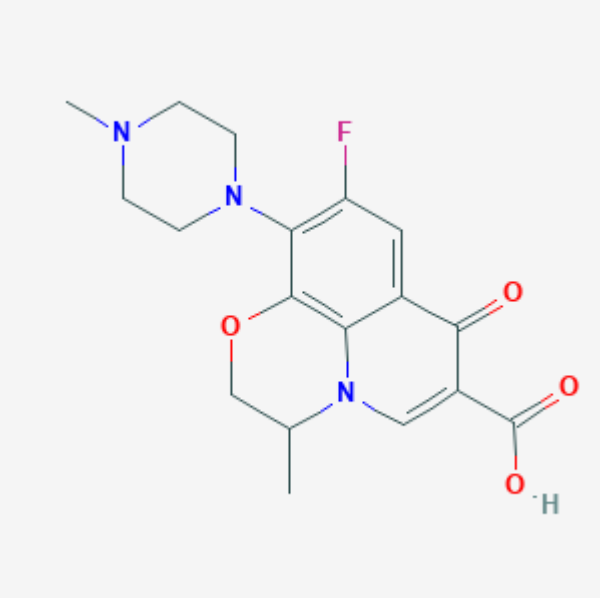
Dexamethasone

Female rabbits (n=6/group) received dexamethasone phosphate (40 mg/mL ophthalmic solution, EGP-437) transscleral to the right eye (OD) using the Eyegate(®) II ocular iontophoresis delivery system once biweekly for 24 consecutive weeks at current doses of 10, 14, and 20 mA-min and current levels up to, and including -4 mA for 3.5-5 min.

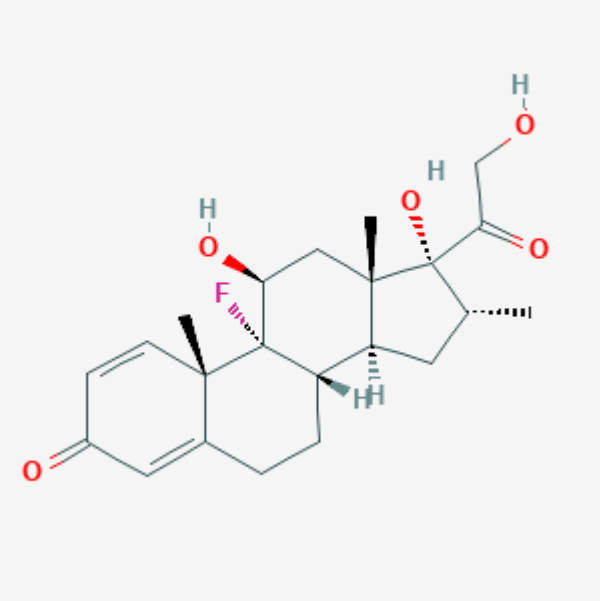
The biweekly transscleral iontophoresis with either the citrate buffer or dexamethasone phosphate at cathodic doses up to and including 20 mA-min and currents up to, and including -4 mA for 24 weeks was well-tolerated. Transient signs of conjunctival hyperemia and chemosis, mild corneal opacity, and fluorescein staining of the cornea were noted and attributed to expected ocular reactions to the temporary placement of the ocular applicator and application of iontophoresis. There was no dexamethasone phosphate-, dexamethasone-, or iontophoresis-related effects on IOP, electroretinography, or histopathology. Reductions in body weight gain, anemia, decreased leukocyte and lymphocyte counts, compromised liver function, enlarged liver, and reduced spleen weight were consistent with systemic corticosteroid-mediated pharmacology, repeated use of anesthesia, stress, and sedentariness, and unlikely to be related to iontophoresis application.

7. Description

Ofloxacin is a fluoroquinolone antibacterial antibiotic. Its chemical name is 7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo[7.3.1.$0^{5,13}$]trideca-5(13),6,8,11-tetraene-11-carboxylic acid. The empirical formula and molecular weight is $C_{18}H_{20}FN_3O_4$ and 361.4 g/mol.



Dexamethasone is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. Its chemical name is (8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one. The empirical formula and molecular weight is $C_{22}H_{29}FO_5$ and 392.5 g/mol.



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

36 months.

8.3 Packaging Information

Oxop-D eye drops is available in 10ml in plastic bottle.

8.4 Storage and handling instructions

Store in cool and dry place.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by CENTAUR PHARMACEUTICALS PVT. LTD. and DCI Pharmaceuticals

11. Details of permission or license number with date

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