Ocupol® Dx

1. **Generic Name**

Polymyxin-B sulfate

Chloramphenicol

Dexamethasone

2. **Qualitative and Quantitative composition**

Each ml of OCUPOL DX DX Eye Drops contains:

Polymyxin-B sulfate 5000 IU

Chloramphenicol 4 mg

Dexamethasone 1mg

Each gm of OCUPOL DX DX Ointment contains:

Polymyxin-B sulfate 10000 IU

Chloramphenicol 10 mg

Dexamethasone 1mg

3. **Dosage form and strength**

Topical ophthalmic solution of OCUPOL DX contains Chloramphenicol (4mg), Polymyxin- B sulfate (5000IU) and Dexamethasone (1mg).
Topical ophthalmic ointment of OCUPOL DX contains Chloramphenicol (10mg), Polymyxin-B sulfate (10000IU) and Dexamethasone (1mg).

4. **Clinical particulars**

4.1 Therapeutic indication

For ocular bacterial infection.

4.2 Posology and method of administration

Eye drops: 1-2 drops twice or thrice a day during daytime.

Ointment: half an inch ribbon of “OCUPOL DX ointment” before sleeping.

4.3 Contraindication

The use of OCUPOL DX is contraindicated in patients:

- With hypersensitivity to any ingredient of the formulations.
- who have experienced bone marrow suppression during previous exposure to chloramphenicol.
- known personal or family history of blood dyscrasias including aplastic anaemia.
- With fungal eye infections.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral infection of cornea or conjunctiva.

4.4 Special warnings and precautions for use

- Chloramphenicol is absorbed systemically from the eye and systemic toxicity has been reported.
- Bone marrow hypoplasia, including aplastic anaemia and death, has been reported following topical use of chloramphenicol. Whilst the hazard is a rare one, it should be borne in mind when assessing the benefits expected from the use of the compound.
- If the eye ointment is to be used on a long-term or intermittent basis, it may be advisable to perform a routine blood profile before therapy and at appropriate intervals thereafter to detect any haemopoietic abnormalities.
- In severe bacterial conjunctivitis and in cases where infection is not confined to the conjunctivae, the topical use of chloramphenicol should be supplemented by appropriate systemic treatment.
- It is recommended that all types of contact lenses be avoided during ocular infections.
- Sensitivity to topically applied aminoglycosides may occur in some patients. Cross-sensitivity to other aminoglycosides may also occur.
- Patients using ophthalmic preparations containing neomycin sulphate should be advised to consult a physician if ocular pain, redness, swelling, or irritation worsens or persists.
- Nephrotoxic and neurotoxic reactions have also occurred with systemic polymyxin B. Although these effects have not been reported following topical ocular use of this product, caution is advised with polymyxin B therapy.
- 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.
- The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).

- Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular 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 discontinued.
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
- Corticosteroids may reduce resistance to and aid in the establishment of non-susceptible bacterial, fungal, parasitic or viral infections and mask the clinical signs of infection or may suppress hypersensitivity reactions to substances in the product. 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.
- Topical ophthalmic corticosteroids may slow corneal wound healing. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 Drug interactions

Concomitant administration of chloramphenicol with other drugs liable to depress bone marrow, hence should be avoided.

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

- Pediatric: Safety and efficacy in children has not been established.

- Geriatric: Safety and efficacy in children has not been established.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.
- Pregnancy and lactation: The safety of topical chloramphenicol in pregnancy and lactation has not been established. Chloramphenicol may be absorbed systemically following the use of eye ointment and may cross the placenta and appear in breast milk. Therefore, this product is not recommended for use during pregnancy and lactation.

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 OCUPOL DX is known.

4.8 Undesirable effects

The adverse reactions reported with OCUPOL DX eye drops/ointment – Periorbital oedema, Ocular hyperaemia, Face oedema, Hypersensitivity.

4.9 Overdose

There is limited experience of overdose with OCUPOL DX. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

Polymyxin B sulfate has a bactericidal action against almost all gram-negative bacilli except the Proteus group. Polymyxin B sulfate interacts with the lipopolysaccharide of the cytoplasmic outer membrane of Gram-negative bacteria, altering membrane permeability and causing cell death. It does not need to enter the cell.

Chloramphenicol is lipid-soluble, allowing it to diffuse through the bacterial cell membrane. It then reversibly binds to the L16 protein of the 50S subunit of bacterial ribosomes, where transfer of amino acids to growing peptide chains is prevented (perhaps by suppression of peptidyl transferase activity), thus inhibiting peptide bond formation and subsequent protein synthesis.

Dexamethasone is a glucocorticoid agonist. Unbound dexamethasone crosses cell membranes and binds with high affinity to specific cytoplasmic glucocorticoid receptors. This complex binds to DNA elements (glucocorticoid response elements) which results in a modification of transcription and, hence, protein synthesis in order to achieve inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema

or scar tissue. The anti-inflammatory actions of dexamethasone are thought to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. susceptible organisms. Chloramphenicol stops bacterial growth by binding to the bacterial ribosome (blocking peptidyl transferase) and inhibiting protein synthesis.

• **Pharmacodynamic properties**

Polymyxin B sulfate is a mixture of polymyxins B1 and B2, obtained from Bacillus polymyxins strains. They are basic polypeptides of about eight amino acids and have cationic detergent action on cell membranes. Polymyxin B is used for infections with gram-negative organisms, but may be neurotoxic and nephrotoxic. All gram-positive bacteria, fungi, and the gram-negative cocci, N. gonorrhoea and N. meningitides, are resistant.

Chloramphenicol is a broad-spectrum antibiotic that was derived from the bacterium Streptomyces Venezuela and is now produced synthetically. Chloramphenicol is effective against a wide variety of microorganisms, but due to serious side-effects (e.g., damage to the bone marrow, including aplastic anaemia) in humans, it is usually reserved for the treatment of serious and life-threatening infections (e.g., typhoid fever). Chloramphenicol is bacteriostatic but may be bactericidal in high concentrations or when used against highly susceptible organisms. Chloramphenicol stops bacterial growth by binding to the bacterial ribosome (blocking peptidyl transferase) and inhibiting protein synthesis.

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.

5.2 Pharmacokinetic properties

Polymyxin B sulfate is not absorbed from the gastrointestinal tract, except in infants who may absorb up to 10% of a dose. It is not absorbed through mucous membranes, or intact or denuded skin. Peak plasma concentrations after intramuscular injection usually occur within 2 hours, but are variable and Polymyxin B sulfate is partially inactivated by serum. It is widely distributed and extensively bound to cell membranes in the tissues; it does not appear to be highly bound to serum proteins. Accumulation may occur after repeated doses. There is no diffusion into the CSF and it does not cross the placenta. Polymyxin B is reported to have a serum half-life of about 6 hours but this is prolonged in renal impairment; values of 2 to 3 days have been reported in patients with a creatinine clearance of less than 10 mL/minute. Polymyxin B sulfate is excreted mainly by the kidneys by glomerular filtration, about 60% of a dose being recovered unchanged in the urine, but there is a time lag of 12 to 24 hours before

Polymyxin B is recovered in the urine. Polymyxin B is not removed to an appreciable extent by peritoneal dialysis or haemodialysis.

Chloramphenicol is active when given orally and, unlike most other antibacterial, it diffuses into the CSF even when the meninges are not inflamed. The majority of a dose is inactivated in the liver, only a small proportion appearing unchanged in the urine.

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.

Excretion

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

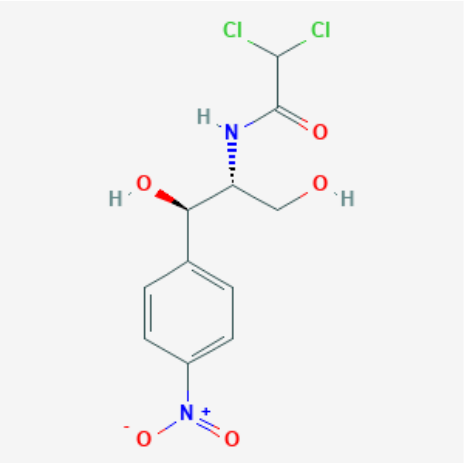
The biweekly transscleral iontophoresis with either the citrate buffer or dexamethasone phosphate at cathodic doses up to and including 20 mA-min and currents up to, and including -4 mA for 24 weeks was well-tolerated. Transient signs of conjunctival hyperemia and chemosis, mild corneal opacity, and 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

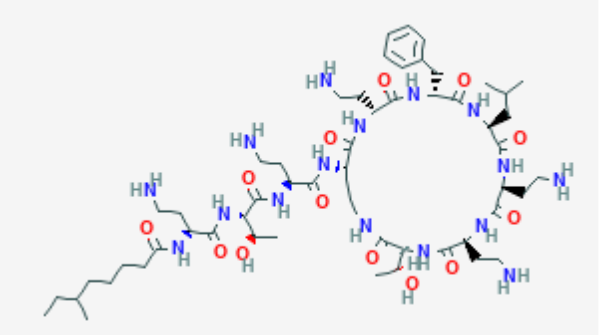
Chloramphenicol

Chloramphenicol is a semisynthetic, broad-spectrum antibiotic derived from Streptomyces venequelae with primarily bacteriostatic activity. The chemical name is 2,2-dichloro-N-[(1R,2R)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide. Its empirical formula and molecular weight is $C_{11}H_{12}Cl_2N_2O_5$ and 323.13 g/mol.



Polymyxin-B sulfate

Polymyxin B is a mixture of the polypeptides polymyxins B1 and B2, both obtained from Bacillus polymyxa strains, with antimicrobial activity. The chemical name is N-[(2S)-4- amino-1-[[(2S,3R)-1-[[(2S)-4-amino-1-oxo-1-[[(3S,6S,9S,12S,15R,18R,21S)-6,9,18-tris(2-aminoethyl)-15-benzyl-3-[(1R)-1-hydroxyethyl]-12-(2-methylpropyl)-2,5,8,11,14,17,20-heptaoxo1,4,7,10,13,16,19-heptazacyclotricos-21-yl]amino]butan-2-yl]amino]-3- hydroxy-1-oxobutan-2-yl]amino]-1-oxobutan-2-yl]-6-methyloctanamide . Its empirical formula and molecular weight is $C_{56}H_{98}N_{16}O_{13}$ and 1203.5 g/mol.



Dexamethasone

Dexamethasone is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. Its chemical name is (8S,9R,10S,11S,13S,14S,16R,17R)-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

OCUPOL DX eye drops- 18 months.

OCUPOL DX eye ointment-24 months.

8.3 Packaging Information

OCUPOL DX Drops is available in 5 ml lupolen vial

OCUPOL DX Ointment is available in a tube of 5 g.

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 4.8

9.3 Dosage

Refer part 4.5

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

158(258)/MFG/DFDA/2013/3541 dated. 29.10.2013 for export.

12. Date of revision: January 2022