

Ocupol[®] Dx

1. Generic Names

Polymyxin-B sulfate

Chloramphenicol

Dexamethasone

2. Qualitative and Quantitative Composition

Each ml of OCUPOL DX Eye Drops contains:

Polymyxin-B sulfate 5000 IU

Chloramphenicol 4 mg

Dexamethasone 1mg

Each gm of OCUPOL 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) and Polymyxin-B sulfate (5000IU).

Topical ophthalmic ointment of OCUPOL DX contains Chloramphenicol (10mg) and Polymyxin-B sulfate (10000IU).

4. Clinical particulars

4.1 Therapeutic indication



We Impart Health to Life

OCUPOL DX is indicated for:

- The treatment of surface ocular infections involving the conjunctiva and/or cornea caused by susceptible organisms.
- For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.
- For the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.
- For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial 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 to obtain a 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.

4.2 Posology and method of administration

As directed by Physician.

4.3 Contraindication

- The use of OCUPOL DX is contraindicated in patients with hypersensitivity to any ingredient of the formulations.
- The use of OCUPOL DX is also contraindicated in epithelial herpes keratitis (dendritic keratitis), vaccinia, varicella other viral diseases of the cornea and conjunctiva, mycobacterial infections 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 OCUPOL DX should be supplemented by appropriate systemic medication.

4.5 Drug interactions

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 efficacy in children has not been established.
- Geriatric: Safety and efficacy in elderly patient 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 topical corticosteroids especially under occlusive dressings include burning sensation, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, and allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae and miliaria.
- Blood dyscrasias have been reported in association with the use of chloramphenicol.
- Chloramphenicol is absorbed systemically from the eye and toxicity has been reported following chronic exposure.
- Bone marrow hypoplasia, including aplastic anaemia and death, has been reported following topical use of chloramphenicol.
- Whilst the hazard is rare, it should be borne in mind when assessing the benefits expected from the use of the compound.
- More serious side effects include hypersensitivity reactions that may present as angioneurotic oedema, urticaria, anaphylaxis, fever, and vesicular and maculopapular dermatitis. If this happens treatment must be discontinued immediately

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.

5.2 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. meningitidis*, 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 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, 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 and they all contribute to its anti-inflammatory effect.

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

- 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 antibacterials, 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 ± 0.9 h.

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

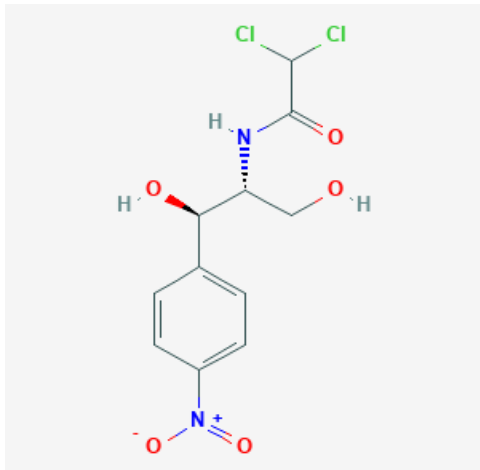
Female rabbits (n=6/group) received dexamethasone phosphate (40 mg/mL ophthalmic solution, EGP-437) transscleral to the right eye (OD) using the Eyegate(®) II ocular iontophoresis delivery system once biweekly for 24 consecutive weeks at current doses of 10, 14, and 20 mA-min and current levels up to,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

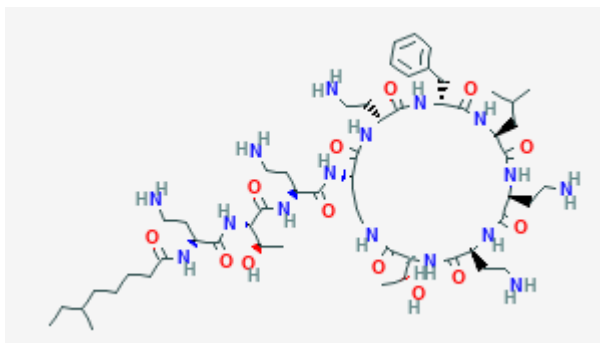
Chloramphenicol

Chloramphenicol is a semisynthetic, broad-spectrum antibiotic derived from *Streptomyces venequelae* with primarily bacteriostatic activity. The chemical name is 2,2-dichloro-*N*-[(1*R*,2*R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide. Its empirical formula and molecular weight is C₁₁H₁₂Cl₂N₂O₅ 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*-[(2*S*)-4-amino-1-[[[(2*S*,3*R*)-1-[[[(2*S*)-4-amino-1-oxo-1-[[[(3*S*,6*S*,9*S*,12*S*,15*R*,18*R*,21*S*)-6,9,18-tris(2-aminoethyl)-15-benzyl-3-[(1*R*)-1-hydroxyethyl]-12-(2-methylpropyl)-2,5,8,11,14,17,20-heptaoxo-1,4,7,10,13,16,19-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 (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.

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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