Ocutob-D

Eye Drops

1. Composition

Each ml of Ocutob-D eye drops contains:

Tobramycin	0.3% w/v
Dexamethasone	0.1% w/v

2. Dosage form and strength

Ocutob-D eye drop is available in 5ml in plastic bottle.

3. Clinical particulars

3.1 Therapeutic indication

Ocutob-D is indicated in ocular infection.

3.2 Posology and method of administration

As directed by physician.

3.3 Contraindication

The use of Ocutob-D is contraindicated in patients with known hypersensitivity to any of the ingredients of the formulation.

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

3.4 Special warnings and precautions for use

- As with other antibiotic preparations, prolonged use with Ocutob-D may result in overgrowth of non-susceptible organisms, including fungi. If super infection occurs, appropriate therapy should be initiated.
- Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to Ocutob-D occurs, discontinue use.
- Use of contact lenses should be discouraged in patients using Ocutob-D.

3.5 Drug interactions

- Tobramycin

Tobramycin has no known severe interactions with other drugs.

- 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.

3.6 Use in special population

- Paediatric: Safety and effectiveness in paediatric patients below the age of 2 years 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: Category B: Reproduction studies in three types of animals at doses up to thirty-three times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the foetus due to tobramycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

  Nursing Mothers: Because of the potential for adverse reactions in nursing infants from Ocutob-D, a decision should be made whether to discontinue nursing the infant or discontinue the drug, taking into account the importance of the drug to the mother.

3.7 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 Ocutob-D eye drop is known.

3.8 Undesirable effects

The most frequent adverse reactions to ocular Tobramycin are hypersensitivity and localized toxicity including lid itching, swelling and conjunctival erythema. If topical ocular Tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

3.9 Overdose

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

4. Pharmacological properties

4.1 Mechanism of action

- Tobramycin

Ocutob-D contain bactericidal aminoglycoside antibiotic Tobramycin. Tobramycin produces its bactericidal action by binding with 30S subunit of the ribosome and inducing misreading of mRNA codons. Ocutob-D has a long post-antibiotic effect, which ensures the persistence of antimicrobial activity even when concentrations have fallen below the minimum inhibitory concentration. The antibacterial spectrum of Ocutob-D includes Staphylococcus aureus, Staphylococcus epidermidis (coagulase-positive and coagulase negative), Streptococci including Group A-beta-hemolytic species and *Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, Proteus vulgaris, Haemophilus influenzae and H. aegyptius*. Ocutob-D is 2-4 times more active against Pseudomonas and Proteus, including those resistant to Gentamicin.

- 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.

4.2 Pharmacodynamic properties

Tobramycin, an aminoglycoside antibiotic obtained from cultures of Streptomyces tenebrarius, is used in combination with other antibiotics to treat urinary tract infections, gynecologic infections, peritonitis, endocarditis, pneumonia, bacteraemia and sepsis, respiratory infections including those associated with cystic fibrosis, osteomyelitis, and diabetic foot and other soft-tissue infections. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. Tobramycin has in vitro activity against a wide range of gram-negative organisms including Pseudomonas aeruginosa.

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.

4.3 Pharmacokinetic properties

- Tobramycin

Tear film concentrations were studied in sixteen (16) healthy male and female subjects who were administered one drop of tobramycin solution in each eye daily for nine (9) consecutive days. It showed a significantly greater area under the tobramycin tear fluid concentration versus time curve (AUCI), a significantly greater area within the tobramycin tear fluid concentration versus time curve exceeding the minimal inhibitory concentration90 (AUC over MIC90), and a greater duration of time over which the tobramycin tear fluid concentrations remained above MIC90.

- Dexamethasone

<u>Absorption</u>

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.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store in cool and dry place.