Tobradex 3mg/ml/1mg/ml eye drops / ear drops, suspension

Therapeutic indications
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older.

Posology and method of administration

Adults: One drop instilled into the conjunctival sac(s) every 4 to 6 hours while the patient is awake. During the initial 24 to 48 hours, the dosage may be increased to one drop every two hours while the patient is awake. Dosing should continue for 14 days not to exceed a maximum of 24 days. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

Paediatric population: Tobradex may be used in children 2 years of age and older at the same dose as in adults.

The safety and efficacy in children younger than 2 years of age have not been established, and no data are available.

Method of administration

Ocular use.

1. Shake the bottle well before use. To prevent contamination of the dropper tip and suspension, care should be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle.
2. Keep the bottle tightly closed when not in use.
3. After cap is removed, if tamper evident snap collar is loose, remove before using product.
4. Gently closing the eyelid (s) and nasolacrimal occlusion for at least 1 minute after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic side effects.
5. In case of concomitant therapy with other topical ophthalmic medicinal products, an interval of 5 minutes should be allowed between successive applications.

Ear use

1. Shake the bottle well before use. To prevent contamination, avoid touching the ear, surrounding areas, or any surfaces with the dropper tip.
2. Keep the bottle tightly closed when not in use.
3. After removing the cap, if the tamper-evident snap collar is loose, remove it before using the product.
4. Administer the drops into the ear canal.
5. This may reduce systemic absorption of the medication and minimize systemic side effects.
6. If using other topical ear drops concurrently, allow a 5-minute interval between applications.

Eye ointments should be administered last.

Contraindications

- Hypersensitivity to tobramycin or dexamethasone
- Herpes simplex keratitis
- Vaccinia, varicella and other viral disease of the cornea and conjunctiva
- Mycobacterial infections of the eye caused by, but not limited to, acid-fast bacilli such as Mycobacterium tuberculosis, Mycobacterium leprae, or Mycobacterium avium.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- Untreated purulent infection of the eye.

Special warnings and precautions for use
- Tobradex is for topical use only and **not** for injection or oral use.
- Prolonged use of topical ophthalmic corticosteroids (i.e. longer than the maximum duration used in clinical trials [24 days]) may result in ocular hypertension/glaucoma with resultant damage to the optic nerve and reduced visual acuity and visual fields defects and may also result in posterior subcapsular cataract formation.

<u>Visual disturbance</u>
- 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.
- It is advisable that the intraocular pressure be checked frequently. This is especially important in paediatric patients receiving dexamethasone-containing products, as the risk of steroid-induced ocular hypertension may be greater in children below 6 years of age and may occur earlier than a steroid response in adults. The frequency and duration of treatment should be carefully considered, and the intraocular pressure should be monitored from the outset of treatment, recognizing the risk for earlier and greater steroid-induced intraocular pressure increases in the paediatric patients.
- 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.
- Prolonged use may also result in secondary ocular infections due to suppression of host response. Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection.
- Sensitivity to topically administered aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalized reactions such as erythema, itching, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If hypersensitivity develops during use of this medicine, treatment should be discontinued.
- Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.
- Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when Tobradex eye drops are used concomitantly with systemic aminoglycosides.
- Caution should be exercised when prescribing Tobradex eye drops to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may aggravate muscle weakness because of their potential effect on neuromuscular function.
- Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy should be discontinued**.**
- Prolonged use of antibiotics such as tobramycin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.
- 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. See section 4.5.
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.

Excipients

- Benzalkonium chloride, used as a preservative in this product, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Benzalkonium chloride may cause eye irritation and discolour soft contact lenses.
- Avoid contact with soft contact lenses. Contact lens wear is not recommended during treatment of an ocular infection or inflammation. If patients are allowed to wear contact lenses, they must be instructed to remove lenses prior to application of Tobradex and wait at least 15 minutes before reinsertion.
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Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions have been described with topical ocular dosing.

Fertility, pregnancy and lactation

Pregnancy: There are no or limited amount of data from the topical ocular use of tobramycin and dexamethasone in pregnant women. Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women. Tobramycin is not expected to cause ototoxicity from in utero exposure. Prolonged or repeated corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Studies in animals have shown reproductive toxicity after systemic administration of tobramycin and dexamethasone. These effects were observed at exposures considered sufficiently in excess of the maximum human ocular dosage delivered from the maternal use of the product (see section 5.3).

Tobradex is not recommended during pregnancy.

Breastfeeding: Tobramycin is excreted in human milk after systemic administration. No data is available on the passage of dexamethasone into human breast milk. It is unknown whether tobramycin and dexamethasone are excreted in human milk following topical ocular administration. It is not likely that the amount of Tobramycin and Dexamethasone would be detectable in human milk or be capable of producing clinical effects in the infant following topical use of the product.

A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility: Studies have not been performed to evaluate the effect of tobramycin on human or animal fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility.

Effects on ability to drive and use machines: Tobradex has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

In clinical studies involving over 1600 patients, Tobradex was administered up to six times daily. No serious ophthalmic or systemic adverse reactions related to Tobradex or components of the combination were reported in clinical studies. The most frequently reported adverse reactions with Tobradex were eye pain, intraocular pressure increased, eye irritation (burning upon instillation) and eye pruritus occurring in less than 1% of patients.

Tabulated list of adverse reactions

The following adverse reactions have been reported with Tobradex during clinical trials or during post marketing experience and are classified

according to the subsequent 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) and very rare (< 1/10,000), and not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

- **Eye disorders:** Uncommon: eye pain, eye pruritus, ocular discomfort, ocular hypertension, conjunctival oedema, increased intraocular pressure, eye irritation
- **Eye disorders:** Rare: keratitis, eye allergy, vision blurred (see also section 4.4), dry eye, ocular hyperaemia
- **Gastrointestinal disorders:** Rare: dysgeusia

Overdose: Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, or in the event of accidental ingestion of the contents of one bottle.

Special precautions for storage
No special precautions for storage

4 weeks after opening bottle it cannot be used any more.