1. NAME OF THE MEDICINAL PRODUCT

TOBRADEX STERILE OPHTHALMIC SUSPENSION

TOBRADEX OPHTHALMIC OINTMENT

TOBRADEX® (Tobramycin® and Dexamethasone) Ophthalmic Suspension and Ointment are sterile, multiple dose antibiotic and steroid combinations for topical ophthalmic use.

2. QUALITATIVE AND QUANTITAVE COMPOSITION

TOBRADEX® ophthalmic suspension

1 mL of suspension contains 3 mg of tobramycin and 1 mg of dexamethasone.

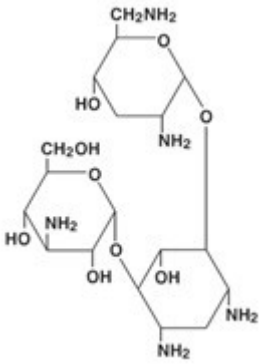
Preservative: 1 mL of suspension contains 0.1 mg benzalkonium chloride.

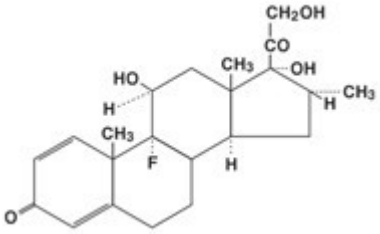
TOBRADEX® ophthalmic ointment

1 gram of ointment contains 3 mg of tobramycin and 1 mg of dexamethasone. Preservative: 1 g of ointment contains 5 mg chlorobutanol.

For the full list of excipients, see section 6.1.

The chemical structures for tobramycin and dexamethasone are presented below:





Empirical Formula : C18H37N5O9 Chemical Name :
0-3-Amino-3-deoxy-α-D-glucopyranosyl-(1-.4)-0-(2,6-diamino-2,3,6-trideoxy-α-D-ribo-hexopyra-nosyl-(1-.6)-2-deoxy-L-streptamine

Empirical Formula : C22H29FO5
Chemical name:
9-Fluoro-11β,17,21-trihydroxy-16αmethylpregna- 1,4-diene-3,20-dione

3. PHARMACEUTICAL FORM

TOBRADEX ophthalmic suspension

Sterile ophthalmic suspension. White to off-white suspension.

TOBRADEX ophthalmic ointment

Sterile ophthalmic ointment.
White to off-white homogeneous ointment

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TOBRADEX® contains tobramycin, an antibiotic, and dexamethasone, a corticosteroid.

TOBRADEX® is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular 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 where the inherent risk of steroid use in certain infective conjunctivitis is accepted 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.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens:

- Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.
- Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.
- *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*. *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and H. aegyptius, *Moraxella lacunata*, and *Acinetobacter calcoaceticus (Herellea vaginacola)* and some *Neisseria* species.

4.2 Posology and method of administration

TOBRADEX® ophthalmic Suspension

Adolescents and adults, including the elderly

1 or 2 drops instilled into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosage may be increased to 1 or 2 drops every 2 hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

Pediatric patients

The safety and efficacy of TOBRADEX® ophthalmic suspension in children have not been established.

Hepatic or renal impairment

The safety and efficacy of TOBRADEX® ophthalmic suspension in patients with hepatic or renal impairment have not been established.

Method of administration

- For ocular use only.
- The bottle must be well shaken before use.
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- Keep the bottle tightly closed when not in use.
- To avoid contamination, the dropper tip should not touch any surface. The tip of the dropper/ tube should also not come into contact with the eye as this may cause injury to the eye.
- Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via ocular route and result in a decrease in systemic adverse reactions.
- If more than one topical ophthalmic medicinal products is being used, the medicines must be administered at least5 minutes apart. Eye ointments should be administered last.

TOBRADEX® ophthalmic ointment

Posology

Apply a small amount (approximately 1cm of the ointment), into the conjunctival sac(s) up to 3 or 4 times daily.

TOBRADEX® ophthalmic ointment may be used at bedtime in conjunction with TOBRADEX ophthalmic suspension used during the day.

Not more than 20 ml or 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in section 4.4.

Pediatric patients

The safety and efficacy of TOBRADEX® ophthalmic ointment in children have not been established.

Hepatic or renal impairment

The safety and efficacy of TOBRADEX® ophthalmic ointment in patients with hepatic or renal impairment have not been established.

Method of administration

- For ocular use only.
- To prevent contamination of the tube tip and ointment, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the tube tip. Keep the tube tightly closed when not in use.
- Do not let the tip of the tube touch your eye.
- Gently closing the eyelid and nasolacrimal occlusion 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.
- In case of concomitant therapy with other topical ocular medicinal products, an interval of 5 minutes should be allowed between successive applications. Eye ointments should be administered last.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Herpes simplex keratitis
- Vaccinia, varicella, and other viral infection of cornea or conjunctiva.
- Mycobacterial ocular infections.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- The use of TOBRADEX® is always contraindicated after uncomplicated removal of a foreign body.

4.4 Special warnings and precautions for use

- NOT FOR INJECTION INTO THE EYE.
- 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, urticaria, 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/Eye Ointment are used concomitantly with systemic aminoglycosides and care should be taken to monitor the total serum concentration.

- Caution should be exercised when prescribing TOBRADEX® Eye Drops/Eye Ointment 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.
- 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.
- Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual field defects, and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure (IOP) should be checked routinely and frequently. This is especially important in paediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. TOBRADEX® is not approved for use in 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 ophthalmic 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).(See Section 4.5). In these cases, treatment should not be discontinued abruptly, but progressively tapered.
- Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections.
- Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral or fungal Infections or parasitic infections and mask the clinical signs of infection.
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
- Fungal infections 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 non-steroidal anti-inflammatory drugs (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.
- Contact lens wear is not recommended during treatment of an ocular inflammation or infection. TOBRADEX ophthalmic suspension contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of TOBRADEX ophthalmic suspension and wait at least 15 minutes before reinsertion.

- When multiple prescriptions are required, or whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

CYP3A4 inhibitors including ritonavir and cobicistat may increase systemic exposure resulting in increased risk of adrenal suppression/Cushing's syndrome (see Section 4.2 Posology and method of administration). The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

If TOBRADEX (topical tobramycin) Eye Drops or Eye Ointment are used while the patient is on a systemic aminoglycoside antibiotic, the patient's total serum aminoglycoside concentration should be monitored. Caution is advised when used concomitantly with any products with potential neurotoxic, ototoxic or nephrotoxic effects.

Do not use TOBRADEX® simultaneously with a topical beta lactam type antibiotic as this is likely to result in inactivation of tobramycin.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data regarding the effects of TOBRADEX® Eye drops and Eye ointment on human or animal fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility. No standard animal fertility studies are available with dexamethasone. Tobramycin did not impair fertility in rats (see Section 5.3 Pre-clinical safety data).

Pregnancy

There are no adequate and well-controlled studies with TOBRADEX® Eye drops and Eye ointment in pregnant women to inform a product-associated risk. Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women.
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.
Embryo-fetal toxicity and teratogenicity were seen in animal studies with dexamethasone, both after systemic and ocular administration at therapeutically relevant dose levels (see Animal data).

Reproductive studies with tobramycin in rats and rabbits have not shown evidence of harm to the fetus following subcutaneous administration at dose levels greater than 45-fold the maximum recommended ocular human dose (MROHD) of 0.288 mg/kg/day based on body surface area (BSA) (see Animal data).
TOBRADEX Eye Drops/Ointment is not recommended during pregnancy.

Data

Human data

Based on data from a paired case-control study, it was concluded that the risk of deafness in children born to mothers who had received gentamicin, neomycin and other aminoglycoside antibiotics during pregnancy cannot be excluded, but the magnitude is estimated to be small. Ototoxicity, which is known to occur after tobramycin therapy, has not been reported as an effect of in utero exposure. However, eighth cranial nerve toxicity in the fetus is well known following exposure to other aminoglycosides and may potentially occur with tobramycin.

Animal data

Dexamethasone

In embryo-fetal development studies, dexamethasone was teratogenic in mice and rabbits following topical ocular application. In mice, rats, and rabbits, a number of fetal malformations, fetal growth retardation, and increased mortality rates were seen at maternally toxic doses following systemic administration (oral, subcutaneous, and intramuscular) during the period of organogenesis. The overall no-observed-effect level (NOEL) for developmental toxicity was derived from an oral rat study and was based on embryotoxicity (0.01 mg/kg/day). This corresponds to less than 1 time the MROHD based on BSA.

Tobramycin

In embryo-fetal development studies in rats and rabbits, pregnant animals received subcutaneous tobramycin during the period of organogenesis at doses up to 100 and 40 mg/kg/day, respectively. There was no embryo-fetal toxicity in either species up to the maximum dose tested corresponding to 56 and 45 times the MROHD based on BSA, respectively.

In a peri- and postnatal development study in rats, subcutaneous administration of up to 100 mg/kg/day tobramycin during early gestation through the lactation period did not adversely affect the fertility index, gestation survival index, litter size, sex distribution, postpartum progeny survival index or weight of offspring. The ratio of the highest dose tested to the MROHD is 56 based on BSA.

Lactation

It is not known if tobramycin and dexamethasone are transferred into human milk following topical ocular administration

Limited published data in lactating women indicate that tobramycin is transferred into human milk following intramuscular 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 ocular use of the product.

However, a risk to the suckling child cannot be excluded. A decision should be made whether to discontinue breastfeeding or to discontinue or abstain from therapy with TOBRADEX® taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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), very rare (<1/10,000).

System Organ Classification	**Adverse reactions**
Eye disorder	*Uncommon*: intraocular pressure increased, eye pain, eye pruritus, ocular discomfort, eye irritation *Rare:* keratitis, eye allergy, vision blurred, dry eye, ocular hyperaemia
Gastrointestinal disorders	*Rare*: dysgeusia

The following adverse drug reactions have been derived from post-marketing experience with TOBRADEX®. Eye drops and Eye ointment via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

System Organ Classification	**Adverse reactions**
Immune system disorders	anaphylactic reaction, hypersensitivity
Nervous system disorders	dizziness, headache
Eye Disorder	eyelid oedema, erythema of eyelid, mydriasis, lacrimation increased
Gastrointestinal disorders	nausea, abdominal discomfort
Skin and subcutaneous tissue disorders	erythema multiforme, swelling of the face, rash, pruritus

Description of selected adverse reactions

- Prolonged use of topical ophthalmic corticosteroids may result in increase of intraocular pressure with possible development of glaucoma, damage to optic nerve, reduced visual activity and visual field defects, posterior subcapsular cataract formation and delayed wound healing (see section 4.4).
- Due to the corticosteroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments (see section 4.4).
- The development of secondary infection has occurred after the use of combinations containing corticosteroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid (see section 4.4).
- Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic tobramycin therapy (see section 4.4).
- Sensitivity to topically administered aminoglycosides may occur in some patients (see section 4.4).

The most frequent adverse reactions to topical ocular tobramycin (TOBRADEX®) are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients.

4.9 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 or tube.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory agents and anti-infectives in combination – corticosteroids and anti-infectives in combination.

ATC code: S01CA01.

Mechanism of action

Aspects of the inflammatory process such as edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, deposition of collagen, scar formation, and fibroblastic proliferation are suppressed. Topical corticosteroids are effective in acute inflammatory conditions of the conjunctiva, sclera, cornea, lids, iris, and anterior segment of the globe as well as in ocular allergic conditions.

Dexamethasone is one of the most potent corticosteroids; it is 5 to 14 times more potent than prednisolone and 25 to 75 times more potent than cortisone and hydrocortisone. The exact mechanism of anti-inflammatory action of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects.

Dexamethasone is a potent corticoid. Corticoids suppress the inflammatory response to a variety of agents and they can delay or slow healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant. Tobramycin is an antibacterial drug. It inhibits the growth of bacteria by inhibiting protein synthesis.

Mechanism of resistance

Resistance to tobramycin occurs by several different mechanisms including (1) alterations of the ribosomal subunit within the bacterial cell; (2) interference with the transport of tobramycin into the cell, and (3) inactivation of tobramycin by an array of adenylylating, phosphorylating, and acetylating enzymes. Genetic information for production of inactivating enzymes may be carried on the bacterial chromosome or on plasmids. Cross resistance to other aminoglycosides may occur.

Breakpoints

The breakpoints and the in vitro spectrum as mentioned below are based on systemic use. These breakpoints might not be applicable on topical ocular use of the medicinal product as higher concentrations are obtained locally and the local physical/chemical circumstances can influence the activity of the product on the site of administration. In accordance with EUCAST, the following breakpoints are defined for tobramycin:

- Enterobacteriaceae S ≤ 2 mg/L, R > 4 mg/L
- Pseudomonas spp. S ≤ 4 mg/L, R > 4 mg/L
- Acinetobacter spp. S ≤ 4 mg/L, R > 4 mg/L
- Staphylococcus spp. S ≤ 1 mg/L, R > 1 mg/L
- Not species-related S ≤ 2 mg/L, R > 4 mg/L

The information listed below gives only an approximate guidance on probabilities whether microorganisms will be susceptible to tobramycin in TOBRADEX® Eye drops and Eye ointment. Bacterial species that have been recovered from external infections of the eye such as observed in conjunctivitis are presented here.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of tobramycin in at least some types of infections is questionable.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. In vitro studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

Pseudomonas aeruginosa, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, and *Acinetobacter calcoaceticus* (*Herellea vaginacola*) and some Neisseria species.

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

Species for which acquired resistance might be a problem

Acinetobacter baumanii, Bacillus cereus, Bacillus thuringiensis, Kocuria rhizophila, Staphylococcus aureus (methicillin resistant – MRSA)*, Staphylococcus haemolyticus (methicillin resistant –MRSH), Staphylococcus, other coagulase-negative spp., Serratia marcescens*

Inherently resistant organisms

Aerobic Gram-positive microorganisms

Enterococcus faecalis, Streptococcus mitis, Streptococcus pneumoniae, Streptococcus sanguis, Chryseobacterium indologenes

Aerobic Gram-negative microorganisms

Haemophilus influenzae, Stenotrophomonas maltophilia

Anaerobic Bacteria

Propionibacterium acnes

5.2 Pharmacokinetic properties

Absorption

Tobramycin is poorly absorbed across the cornea and conjunctiva when administered by topical ocular route. A peak concentration of 3 micrograms/mL in aqueous humor after 2 hours was attained followed by a rapid decline after topical administration of 0.3% tobramycin. However, TOBRADEX® delivers 542 ± 425 micrograms/mL tobramycin in human tears at 2 minutes after ocular dosing, a concentration that generally exceeds the MIC of the most resistant isolates (MICs > 64 micrograms/mL).

Peak dexamethasone concentrations in aqueous humor after administration of TOBRADEX Eye drops and Eye ointment were attained approximately at 2 hours with a mean value 32 ng/mL.

Systemic absorption of tobramycin after TOBRADEX Eye drops and Eye ointment administration was poor with plasma concentrations generally below the limit of quantitation.

Plasma concentrations of dexamethasone was observed but were very low with all values less than 1 ng/mL after TOBRADEX Eye drops and Eye ointment administration.

The bioavailability of oral dexamethasone ranged from 70 to 80% in normal subjects and patients.

Distribution

For tobramycin, systemic volume of distribution is 0.26 L/kg in man. Human plasma protein binding of tobramycin is low at less than 10%.

For dexamethasone, the volume of distribution at steady state was 0.58 L/kg after intravenous administration. The plasma protein binding of dexamethasone is 77%.

Biotransformation

Tobramycin is not metabolized while dexamethasone is principally metabolized to 6betahydroxydexamethasone along with the minor metabolite, 6beta-hydroxy-20-diydrodexamethasone.

Elimination

Tobramycin is excreted rapidly and extensively in the urine via glomerular filtration, and primarily as unchanged drug. Systemic tobramycin clearance was 1.43 ± 0.34 mL/min/kg for normal weight patients after intravenous administration and its systemic clearance decreased proportionally to renal function. The half-life for tobramycin is approximately 2 hours.

With dexamethasone after intravenous administration, the systemic clearance was 0.125 L/hr/kg with 2.6% of the dose recovered as unchanged parent drug while 70% of the dose was recovered as metabolites. The half-life has been reported as 3 to 4 hours but was found to be slightly longer in males. This observed difference was not attributed to changes in dexamethasone systemic clearance but to differences in volume of distribution and body weight.

Linearity/non-linearity

Ocular or systemic exposure with increasing dosing concentrations of tobramycin after topical ocular administration of tobramycin has not been tested. Therefore, the linearity of exposure with topical ocular dose could not be established. Mean Cmax for dexamethasone at a topical ocular dose concentration of 0.033% with 0.3% tobramycin appeared lower than with Tobradex with a value of approximately 25 ng/mL but this decrease was not proportional to dose.

PK/PD relationship

A specific PK/PD relationship has not been established for TOBRADEX® Eye drops and Eye ointment. Dexamethasone has demonstrated dose-independent pharmacokinetics in published animal studies.

Published in vitro and in vivo studies have shown that tobramycin features a prolonged post-antibiotic effect, which effectively suppresses bacterial growth despite low serum concentrations. Systemic administration studies of tobramycin have reported higher maximum concentrations with once daily compared to multiple daily dosing regimens. However, the weight of current evidence suggests that once daily systemic dosing is equally as efficacious as multiple-daily dosing. Tobramycin exhibits a concentration-dependent antimicrobial kill and greater efficacy with increasing levels of antibiotic above the MIC or minimum bactericidal concentration (MBC).

Hepatic and renal impaired

The pharmacokinetics of tobramycin or dexamethasone with TOBRADEX® administration has not been studied in these patient populations.

Effect of age on pharmacokinetics

There is no change in tobramycin pharmacokinetics in older patients when compared to younger adults. No correlation between age and plasma concentrations of dexamethasone was observed after oral administration of dexamethasone as well.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans from topical ocular exposure to tobramycin or dexamethasone based on repeated-dose topical ocular toxicity and genotoxicity studies. No carcinogenicity studies are available with dexamethasone. In a 2-year inhalation study in rats with tobramycin, no carcinogenic effect was observed up to the highest dose of 25.7 mg/kg/day,

corresponding to 14 times the MROHD based on BSA.For information on developmental toxicity studies, (see Section 4.6 Fertility, pregnancy and lactation).

In standard fertility studies, subcutaneous administration of tobramycin up to 100 mg/kg/day did not impair fertility in rats, corresponding to 56 times the MROHD, based on BSA. No standard fertility studies have been conducted with dexamethasone. In a non-standard study, dexamethasone enhanced fertility in a gonadotropin-primed, immature rat model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TOBRADEX® ophthalmic suspension

Benzalkonium chloride, tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sulfuric acid and/or sodium hydroxide (to adjust pH) and purified water.

TOBRADEX® ophthalmic ointment

Chlorobutanol, liquid paraffin, and vaseline

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Up to 24 months

Discard 4 weeks after opening.

6.4 Special precautions for storage

TOBRADEX® ophthalmic suspension

Do not store above 30 °C.

DO NOT FREEZE

Shake well before using.

Do not use this medicine after the expiry date which is stated on the packaging. T OBRADEX® Eye drops must be kept out of the sight and reach of children. Discard 4 weeks after first opening

TOBRADEX® ophthalmic ointment

Do not store above 25 °C.

Do not use this medicine after the expiry date which is stated on the packaging. T OBRADEX® Eye Ointment must be kept out of the sight and reach of children. Discard 4 weeks after first opening

6.5 Nature and contents of container

TOBRADEX® ophthalmic suspension:

Plastic bottle containing 5 mL.

TOBRADEX® ophthalmic ointment:

Tube containing 3.5 g.

Not all preparations may be available commercially.

6.6 Instructions for use and handling and disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 Manufacturer

See folding box

(Information Issued: May 2021 .SIN)

Novartis Pharma AG, Basel, Switzerland