SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

TOBRADEX* 3mg/ml/1mg/ml Eye Drops, Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains: Tobramycin 3mg Dexamethasone 1mg.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye Drops, Suspension.
White to off-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 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.

Use in the Elderly:
Clinical studies have indicated dosage modifications are not required for use in the elderly.

Paediatric population:
TOBRADEX may be used in children 2 years of age and older at the same dose as in adults. Currently available data is described in section 5.1.

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

Use in hepatic and renal impairment:
TOBRADEX has not been studied in these patient populations

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. Keep the bottle tightly closed when not in use. After cap is removed, if tamper evident snap collar is loose, remove before using product.

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.

In case of concomitant therapy with other topical ophthalmic medicinal products, an interval of 5 minutes should be allowed between successive applications.

Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to tobramycin or dexamethasone or to any of the excipients listed in section 6.1.
- 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.

4.4 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.

Visual disturbance
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.

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.

The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).

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 used concomitantly.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Dexamethasone is metabolized via cytochrome P450 3A4 (CYP3A4). CYP3A4 inhibitors (including ritonavir and cobicistat); may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. 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.

4.6 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.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

TOBRADEX has no or negligible influence on the ability to drive and use machines.
No studies on the effects on the ability to drive and use machines have been performed. As with any eye drop, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

4.8 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.

System organ classification	Frequency	Adverse reaction
Immune system disorders	Not known	anaphylactic reaction, hypersensitivity
Endocrine disorders	Not known	Cushing's syndrome, adrenal suppression (see section 4.4)

Nervous system disorders	Uncommon Not known	headache dizziness
Eye disorders	Uncommon Rare Not known	eye pain, eye pruritus, ocular discomfort, ocular hypertension, conjunctival oedema, increased intraocular pressure, eye irritation keratitis, eye allergy, vision blurred (see also section 4.4), dry eye, ocular hyperaemia eyelid oedema, erythema of the eyelid, mydriasis, lacrimation increased
Respiratory, thoracic, and mediastinal disorders	Uncommon	rhinorrhoea, laryngospasm
Gastrointestinal disorders	Rare Not known	dysgeusia nausea, abdominal discomfort
Skin and subcutaneous tissue disorders	Not known	erythema multiforme, rash, swelling face, pruritus

Description of selected adverse reactions
The following adverse reactions have been observed following use with Dexamethasone ophthalmic suspension:

System organ classification	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	headache
Eye disorders	Common	eye irritation,* ocular hyperaemia,* erythema of eyelid, abnormal sensation in eye*
Respiratory, thoracic, and mediastinal disorders	Common	post nasal drip

The following adverse reactions have been observed following use with Tobramycin ophthalmic solution:

System organ classification	**Frequency**	**Adverse reaction**
Eye disorders	Common Uncommon	ocular hyperaemia,* eye pain* eye pruritus,* ocular discomfort,* eye allergy, eyelid oedema,* conjunctivitis,* glare, increased lacrimation,* keratitis*

* These adverse reactions were also observed with TOBRADEX during post marketing.

Prolonged use of topical ophthalmic corticosteroids may result in increased intraocular pressure with damage to the optic nerve, reduced visual acuity and visual field defects, posterior subcapsular cataract formation and delayed wound healing.

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 steroids.

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).

--To reports any side effect(s):

- ***Saudi Arabia:***

--The National Pharmacovigilance and Drug Safety Centre (NPC)
o Fax: +966-11-205-7662
o Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
o Toll free phone: 8002490000
o E-mail: npc.drug@sfda.gov.sa
o Website: www.sfda.gov.sa/npc

- ***Other GCC States:***

-- Please contact the relevant competent authority.

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. A topical overdose of TOBRADEX may be flushed from the eye(s) with lukewarm tap water.

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: S01C A01.

Dexamethasone:
The efficacy of corticosteroids for the treatment of inflammatory conditions of the eye is well established. Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules, cyclooxygenase I or II, and cytokine expression. This action culminates in a reduced expression of pro-inflammatory mediators and the suppression of adhesion of circulating leukocytes to the vascular endothelium, thereby preventing their migration into inflamed ocular tissue. Dexamethasone has marked anti-inflammatory activity with reduced mineralocorticoid activity compared with some other steroids, and is one of the most potent anti-inflammatory agents.

Tobramycin:
Tobramycin is a potent, broad-spectrum, rapidly bactericidal aminoglycoside antibiotic. It exerts its primary effect on bacterial cells by inhibiting polypeptide assembly and synthesis on the ribosome. Tobramycin in this combination provides antibacterial protection against susceptible bacteria.

The following MIC breakpoints, separating susceptible from intermediate susceptible organisms, and intermediate susceptible from resistant organisms, are suggested: S ($\leq$ 4 μg/ml, R ($\geq$ 8 μg/ml). The prevalence of 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 the agent in at least some types of infections is questionable. The following information gives only an approximate guidance on probabilities whether bacteria will be susceptible to tobramycin in TOBRADEX.

The breakpoint definitions classifying isolates as susceptible or resistant are useful in predicting clinical efficacy of antibiotics that are administered systemically. However, when the antibiotic is administered in very high concentrations topically directly on the site of infection, these breakpoint definitions may not be applicable. Most isolates that would be classified as resistant by systemic breakpoints are indeed successfully treated topically.

In vitro studies have shown tobramycin to be active against most strains of common ocular pathogens and common skin flora bacteria as listed in the Table below:

Categories	**Frequency of Acquired Resistance in Europe**
SENSITIVE SPECIES ***Aerobic Gram-Positive Microorganisms*** *Corynebacterium species* *Staphylococcus aureus* Methicillin -S [a] *Staphylococcus epidermidis* Methicillin -S [a] Other Coagulase-negative Staphylococci	 0-3% 0-3% 0-28% 0-40%
Aerobic Gram-Negative Microorganisms *Acinetobacter species* *Citrobacter species* *Escherichia coli* *Enterobacter species* *Haemophilus influenzae* *Klebsiella species* *Moraxella species* *Proteus species* *Pseudomonas aeruginosa*	 0% 0% 0% 0% 0% 0% 0% 0% 0%
MODERATELY SUSCEPTIBLE SPECIES **(*in vitro*, intermediate susceptibility)** ***Aerobic Gram-Negative Microorganisms*** *Serratia marcescens*	
INHERENTLY RESISTANT SPECIES ***Aerobic Gram-Positive Microorganisms*** *Enterococcus species* *Staphylococcus aureus* Methicillin –R [a] *Staphylococcus epidermidis* Methicillin –R [a] *Streptococcus pneumoniae* *Streptococcus species*	 50 – 70% 30 – 40%
Aerobic Gram-Negative Microorganisms *Burkholderia cepacia* *Stenotrophomonas maltophilia*	
Anaerobic microorganisms Strict anaerobic bacteria	
Others *Chlamydia species* *Mycoplasma species* *Rickettsia species*	

[a] Methicillin-susceptible (S), Methicillin-resistant (R). The beta-lactam (i.e., methicillin; penicillin) resistance phenotype is unrelated to the aminoglycoside resistance phenotype and both are unrelated to the virulence phenotypes. Some methicillin-resistant (R) *S. aureus* strains (MRSA) are susceptible to tobramycin (MIC: S $\leq$4); conversely some strains of methicillin–susceptible (S) *S. aureus* (MSSA) are resistant to tobramycin (MIC: S $\geq$8)

The frequency of methicillin resistance (R) may be up to 50 % of all staphylococci in some European countries.

Paediatric Population

The safety and efficacy of TOBRADEX in children have been established by broad clinical experience, but only limited data are available. In a clinical study of TOBRADEX suspension for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of TOBRADEX every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

Other information
Cross-resistance between aminoglycosides (e.g., gentamicin and tobramycin) is due to the specificity of the enzyme modifications, Adenyltransferase (ANT) and Acetyltransferase (ACC). However, cross-resistance varies between the aminoglycoside antibiotics due to the differing specificity of the various modifying enzymes. The most common mechanism of acquired resistance to aminoglycosides is antibiotic inactivation by plasmid and transposon-encoded modifying enzymes.

5.2 Pharmacokinetic properties

Tobramycin:
Animal studies have shown that tobramycin is absorbed into the cornea following ocular administration. Following systemic administration to patients with normal renal function, a plasma half-life of approximately 2 hours has been observed. Tobramycin is eliminated almost exclusively by glomerular filtration with little if any biotransformation. Plasma concentrations of tobramycin following the 2-day topical ocular regimen of TOBRADEX were below the limit of quantification in most subjects or low (≤0.25 microgram/ml).

Dexamethasone:
Following ocular administration, dexamethasone is absorbed into the eye with maximum concentrations in the cornea and aqueous humour attained within 1-2 hours. The plasma half-life of dexamethasone is approximately 3 hours. Dexamethasone is eliminated extensively as metabolites. Systemic exposure to dexamethasone is low following topical ocular administration of TOBRADEX. Peak dexamethasone plasma levels after the last topical dose ranged from 220 to 888pg/ml (mean 555 ± 217pg/ml) after administration of one drop of TOBRADEX to each eye four times per day for two consecutive days.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans from topical ocular exposure to tobramycin or dexamethasone based on conventional repeated-dose topical ocular toxicity studies, genotoxicity or carcinogenicity studies. Effects in non-clinical reproductive and developmental studies with tobramycin and dexamethasone were observed only at exposures considered sufficiently in excess of the maximum human ocular dosage indicating little relevance to clinical use for low-dose short-term courses of therapy.

Tobramycin has not been shown to induce teratogenicity in rats or rabbits. The ocular administration of 0.1% dexamethasone resulted in fetal anomalies in rabbits. Dexamethasone had no adverse effects on female fertility in a chorionic gonadotropin primed rat model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Hydroxyethylcellulose
Benzalkonium chloride
Purified water
Sodium chloride
Sodium sulphate anhydrous
Sulphuric acid for pH adjustment and / or
Sodium hydroxide for pH adjustment
Tyloxapol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After the first opening of the container, the sterile ophthalmic suspension should not be used longer than four weeks.

6.4 Special precautions for storage

Do not store above 30°C. Discard 4 weeks after first opening. Shake Well
Before Using".

6.5 Nature and contents of container

DROPTAINER* dispenser containing 5 ml, White LDPE bottles with LDPE dispensing plug and PP closure.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Novartis Pharma AG
Lichtstrasse 35 Basle,
Switzerland

8. MARKETING AUTHORISATION NUMBER(S)

10-140-94

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 1994
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

09/17

* a trademark of Novartis