NOVARTIS

Regulatory Affairs

TOBRADEX® (tobramycin 3 mg/mL – dexamethasone 1 mg/mL) Eye drops, suspension

TOBRADEX® (tobramycin 3 mg/mL – dexamethasone 0.5 mg/mL) Eye drops, suspension

TOBRADEX® (tobramycin 3 mg/g – dexamethasone 1 mg/g) Eye ointment

Core Data Sheet (CDS)

Version 3.1

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosage regimen, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

Effective date:	22-Mar-2019
Safety Label Change (SLC) Tracking Number:	2019-PSB/GLC-0958-s
Document status:	Final

1 NAME OF THE MEDICINAL PRODUCT

TOBRADEX® Eye Drops, Suspension or

TOBRAMYCIN, DEXAMETHASONE FALCON® Eye Drops, or

TOBRASONE® Eye Drops, Suspension

TOBRADEX® Eye Ointment, or

TOBRAMYCIN, DEXAMETHASONE FALCON® Eye Ointment, or

TOBRASONE® Eye Ointment

* *Alternative names may be applicable. Refer to the currently approved product labeling.*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tobradex® (tobramycin 3 mg/mL-dexamethasone 1 mg/mL) Eye Drops Suspension:

Active: 1 mL of suspension contains 3 mg of tobramycin and 1 mg of dexamethasone

Preservative: benzalkonium chloride (0.01%).

Excipients: See section 6.1

Tobradex (tobramycin 3 mg/mL - dexamethasone 0.5 mg/mL) Eye Drops, Suspension

Active: 1 mL of suspension contains 3 mg of tobramycin and 0.5 mg of dexamethasone

Preservative: benzalkonium chloride (0.01%).

Excipients: See section 6.1

Tobradex (tobramycin 3 mg/mL - dexamethasone 1 mg/g) Eye Ointment

Active: 1 g ointment contains 3 mg of tobramycin and 1 mg of dexamethasone

Preservative: chlorobutanol, anhydrous (0.5%),

Excipients: See section 6.1

* *Refer to the currently approved product labeling.*

3 PHARMACEUTICAL FORM

Eye Drops, suspension: white to off-white suspension

Eye Ointment: white to off-white homogeneous ointment

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Tobradex Eye Drops is indicated for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older [1].
- Tobradex Eye Ointment 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 [1].
- 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 conjunctivitides 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 [1].
- 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 [1].

**Refer to local labeling. Indications and patient population are per local approval.*

4.2 Posology and method of administration

Adolescents and adults, including the elderly

Tobradex Eye Drops [1]

- One or two drops instilled into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dose may be increased to one or two drops every two hours. Frequency should be decreased gradually as warranted by the improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.
- In severe disease, one or two drops instilled every hour until inflammation is controlled, and gradually decrease frequency to one or two drops every two hours during 3 days; thereafter, one to two drops every 4 hours during 5 to 8 days, and finally one to two drops every day during the 5 to 8 last days, if considered necessary.
- Following cataract surgery, the dose is one drop instilled four times a day, from the day after surgery for up to 24 days. Treatment can be started the day before surgery with one drop four times a day, continuing with one drop after surgery, and then four times a day for up to 23 days. If needed, the frequency can be increased up to one drop every two hours for the first two days of therapy.

- It is advisable that the intraocular pressure be routinely monitored.

Tobradex Eye Ointment [1]

- Apply a small amount (approximately 1⁄2 inch ribbon) into the conjunctival sac(s) up to 3 or 4 times daily.
- May be used adjunctively with drops at bedtime.

Pediatric patients [1]

- 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 are available.

Hepatic and renal impairment [1]

- Tobradex has not been studied in these patient populations. However, due to low systemic absorption of tobramycin and dexamethasone after topical administration of this product, dose adjustment is not necessary.

Method of administration [1]

- For ocular use only
- After cap is removed, if tamper evident snap collar is loose, remove before using product.
- The bottle must be well shaken before use.
- To prevent contamination of the dropper tip and eye drops, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle *[Tobradex Eye Drops]*.
- Do not let the tip of the tube touch your eye *[Tobradex Eye Ointment]*.
- 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.

**Refer to local labeling. Posology and patient population are per local approval.*

4.3 Contraindications [1]

- Hypersensitivity to the active substances or to any of the excipients.
- Herpes simplex keratitis.

- Vaccinia, varicella, and other viral infection of cornea or conjunctiva.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- Mycobacterial ocular infections.

4.4 Special warnings and precautions for use

- 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. *[Information to be included under Section 4.2]* [1].
- 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 [1].
- 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 [1].
- 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 [1,2].
- 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 [2].
- 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 should be checked routinely and frequently. *[FOR COUNTRIES THAT HAVE PEDIATRIC USE INCLUDED OR APPROVED IN THE LOCAL LABEL:]* <This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults>. *[FOR COUNTRIES THAT HAVE PEDIATRIC USE EXCLUDED OR CONTRA-INDICATED IN THE LOCAL LABEL:]* <This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. *[TRADENAME]* is not approved for use in pediatric patients>. The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes) [1].

- 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 [1].
- Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral or fungal or parasitic infections and mask the clinical signs of infection [1].
- Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy should be discontinued [1].
- 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 [1].
- 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) [1].
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids [1].
- Contact lens wear is not recommended during treatment of an ocular inflammation or infection. Tobradex Eye Drops contains benzalkonium chloride which may cause eye irritation and is known to discolor 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 Eye Drops and wait at least 15 minutes before reinsertion. *[Only for products containing benzalkonium chloride]* [1].

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 [1].
- CYP3A4 inhibitors including ritonavir and cobicistat may increase systemic exposure resulting in increased risk of adrenal suppression/Cushing's syndrome. (See Section 4.4). 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 [1].

4.6 Fertility, pregnancy and lactation

Fertility [1]

Studies have not been conducted 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.

Dexamethasone was free of adverse effects on fertility in a chorionic gonadotropin primed rat model.

Pregnancy [1]

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. 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 (see Section 5.3).

Tobradex Eye drops/Ointment is not recommended during pregnancy.

Lactation [1]

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 breastfed 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.

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 [1].

4.8 Undesirable effects

The following adverse reactions have been reported during clinical trials with Tobradex Eye Drops/Ointment 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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness [1].

System organ classification	Adverse reactions
Eye disorders	*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

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data [1].

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

Additional adverse reactions reported with the individual components of Tobradex Eye Drops/Ointment are listed in the product information for Maxidex Eye Drops and/or Eye Ointmentand Tobrex/Tobrex 2X Eye Drops and/or Tobrex Eye Ointment [1].

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 [1].

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory agents and antiinfectives in combination; corticosteroids and antiinfectives in combination.

ATC code: S01CA01 [1]

Mechanism of action [1]

Topical corticosteroids exert an anti-inflammatory action and have been used for the treatment for anterior inflammation since the 1950s. 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. Of paramount importance with regard to local therapy is the fact that dexamethasone is over 2,000 times more soluble than hydrocortisone or prednisolone. 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 [1]

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 [1]

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

Clinical efficacy against specific pathogens

The information listed below gives only an approximate guidance on probabilities whether microorganisms will be susceptible to tobramycin in Tobradex. Bacterial species that have been recovered from external ocular 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.

COMMONLY SUSCEPTIBLE SPECIES

- Aerobic Gram-positive microorganisms:
- Bacillus megaterium
- Bacillus pumilus
- Corynebacterium macginleyi
- Corynebacterium pseudodiphtheriticum
- Kocuria kristinae
- Staphylococcus aureus (methicillin susceptible – MSSA)
- Staphylococcus epidermidis (coagulase-positive and –negative)
- Staphylococcus haemolyticus (methicillin susceptible – MSSH)
- Streptococci (inlcuding some of the group A beta-hemolytic species, some nonhemo-lytic species, and some Streptococcus pneumoniae

Aerobic Gram-negative microorganisms :

- Acinetobacter calcoaceticus
- Acinetobacter junii
- Acinetobacter ursingii
- Citrobacter koseri
- Enterobacter aerogenes
- Escherichia coli
- H. aegyptius
- Haemophilus influenzae
- Klebsiella oxytoca
- Klebsiella pneumoniae
- Morganella morganii
- Moraxella catarrhalis
- Moraxella lacunata
- Moraxella oslonensis
- Some Neisseria species
- Proteus mirabilis
- Most Proteus vulgaris strains
- Pseudomonas aeruginosa
- Serratia liquifaciens

Anti-bacterial activity against other relevant pathogens

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

Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin.

PK/PD relationship [1]

A specific PK/PD relationship has not been established for Tobradex. 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).

Data from clinical studies [1]

Pharmacodynamic clinical trials of cumulative safety data from clinical studies are presented in Section 4.8.

Pediatric patients [1]

The safety and efficacy of Tobradex in children have been established by broad clinical experience, but only limited data are available.

Geriatric patients [1]

No overall clinical differences in safety or efficacy have been observed between the elderly and other adult populations.

5.2 Pharmacokinetic properties [1]

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 were attained approximately at 2 hours with a mean value 32 ng/mL.

Systemic absorption of tobramycin after Tobradex 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 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 6beta-hydroxydexamethasone 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 C_{max} 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.

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.

Pediatric patients

Aminoglycosides including topical ocular tobramycin has been commonly used among children, infants and neonates to treat serious Gram-negative infections. Clinical pharmacology of tobramycin in children has been described after systemic administration. Dexamethasone pharmacokinetics in pediatrics appears not to differ from adults after intravenous dosing.

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 [1].

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tobradex (tobramycin 3 mg/mL - dexamethasone 1 mg/mL) Eye Drops, Suspension
Benzalkonium chloride
Tyloxapol

Disodium edetate
Sodium chloride
Hydroxyethylcellulose
Sodium sulphate, anhydrous
Sulphuric acid and/or sodium hydroxide (to adjust pH)
Purified water

Tobradex (tobramycin 3 mg/mL - dexamethasone 0.5 mg/mL) Eye Drops, Suspension
Benzalkonium chloride
Xanthan gum
Tyloxapol
Disodium Edetate
Sodium chloride
Propylene glycol
Sodium sulfate
Hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

Tobradex (tobramycin 3 mg/g - dexamethasone 1 mg/g) Eye Ointment
Chlorobutanol, anhydrous
Liquid paraffin
White soft paraffin

** Information might differ in some countries. Refer local labeling.*

6.2 Incompatibilities

Not applicable.

** Information might differ in some countries. Refer local labeling.*

6.3 Shelf life

Up to 24 months

Discard 4 weeks after first opening.

** Information might differ in some countries. Refer local labeling.*

6.4 Special precautions for storage

Eye drops: Do not store above 30°C. Store upright. Do not freeze.

Eye ointment: Store at 8 to 27°C .Do not refrigerate.

** Information might differ in some countries. Refer local labeling.*

6.5 Nature and contents of container

Eye drops: 1 mL, 2.5 mL, 5 mL, 10 mL, 15 mL low density polyethylene dropper bottle.

Eye ointment: 3.5 g aluminum tube

** Information might differ in some countries or for different fill sizes / presentations. Refer to local labeling.*

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.

7 REFERENCES

1) CCDS Supporting Document: TDOC-0050775 v.2.0. This is the supporting document for the previous CCDS version (TDOC-0050774 v.3.0).

Newly added reference CDS Amendment v3.1 – 22-Mar-2019

2) 2.5 Clinical Overview Labeling Change Rationale for changes to Core Data Sheet (CDS) - Product Information Warnings and Precautions “Neuromuscular disorders”. Novartis. Mar-2019.

8 CDS history table

Version	Effective date	GLC/PSB approval date	SLC Tracking No.	Section keyword	Refs.	Author(s) GLM/GPRD/ GPRM
1.0	01-Sep-2015	24-Aug-2015	N/A	New CDS		Lauren Langis
2.0	19-Jan-2016	15-Dec-2015	TDOC-0050774 v.2.0-s	Amendment		Lauren Langis
				Section 4.4: new warning on hypersensitivity		
				Section 4.8: new ADRs anaphylactic reaction, erythema multiforme		
3.0	21-Jan-2018	28-Nov-2017	TDOC-0050774 v.3.0-s	Amendment	1	Lauren Langis
				Section 4.4: new warning on CYP3A4 inhibitors		
				Section 4.5: new interaction CYP3A4 inhibitors, adrenal suppression, Cushing’s syndrome		
3.1	22-Mar-2019	29-Jan-2018	2019-PSB/GLC-0958-s	Amendment	2	Betty Lan
				Section 4.4: new warning on myasthenia gravis, systemic aminoglycosides		