PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNETILDEX®

Netilmicin and Dexamethasone Ophthalmic Solution with Preservative
Solution, 0.3% (w/v) netilmicin (as netilmicin sulfate) and 0.1% (w/v) dexamethasone (as dexamethasone sodium phosphate), ophthalmic

Netilmicin and Dexamethasone Preservative-free Ophthalmic Solution
Solution, 0.3% (w/v) netilmicin (as netilmicin sulfate) and 0.1% (w/v) dexamethasone (as dexamethasone sodium phosphate), ophthalmic

Antibacterial and Corticosteroid

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RECENT MAJOR LABEL CHANGES

N/A

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PrNETILDEX® (netilmicin and dexamethasone ophthalmic solution) is indicated in adult patients (including the elderly) for the treatment of inflammatory ocular conditions of the anterior segment of the eye following cataract surgery where adjunct topical therapy to reduce the risk of bacterial infection is appropriate.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NETILDEX and other antibacterial drugs, NETILDEX should be used only to reduce the risk of infections that are proven or strongly suspected to be caused by susceptible bacteria.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

2 CONTRAINDICATIONS

NETILDEX is contraindicated in:

- Known or suspected hypersensitivity to netilmicin or other aminoglycosides, dexamethasone or other corticosteroids, or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Herpes simplex keratitis or other Herpes simplex eye infections.
- Vaccinia, varicella, and other viral diseases of the cornea and conjunctiva.
- Fungal diseases of the eye or untreated parasitic eye infections.
- Mycobacterial ocular infections, including tuberculosis of the eye.
- Acute purulent untreated infections of the eye which may be masked or enhanced by the presence of a corticosteroid.
- After uncomplicated removal of a corneal foreign body.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

For topical ophthalmic use only. Not for injection into the eye. Not for otic use. Not for nasal use.

3.2 Recommended Dose and Dosage Adjustment

Instill one drop of NETILDEX into the conjunctival sac of the affected eye, four times daily for 7 days.

Health Canada has not authorized an indication for pediatric use (<18 years of age).

3.3 Administration

NETILDEX ophthalmic solution with preservative

Ensure that the tip of the container does not touch the eye or any other surface. Close the container immediately after use. Discard the container and any unused content 28 days after first opening.

NETILDEX preservative-free ophthalmic solution

Ensure the preservative-free container is not damaged before use. Use immediately after opening. After administration, discard the container and any unused content.

If concurrent use of NETILDEX and soft contact lenses is necessary, it is advised to use NETILDEX preservative-free ophthalmic solution. Remove contact lenses prior to administration and wait at least 15 minutes after administration before re-insertion. (see **WARNINGS AND PRECAUTIONS**).

If more than one topical ophthalmic product is being used by the patient, the administrations should be at least ten minutes apart.

3.4 Missed Dose

If a dose of this medication is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and return to the regular dosing schedule. Do not use a double dose to make up for the missed dose.

4 OVERDOSAGE

Overdosage in the use of topical ophthalmic preparations is a remote possibility. An ophthalmic overdose may be flushed from the eye(s) with warm water.

Discontinue medication when heavy or protracted use is suspected.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Topical ophthalmic	Solution with preservative / 0.3% (w/v) netilmicin (as netilmicin sulfate) and 0.1% (w/v) dexamethasone (as dexamethasone sodium phosphate)	Benzalkonium chloride (0.005%) as preservative, disodium phosphate dodecahydrate, monobasic sodium phosphate, purified water, sodium citrate.
	Preservative-free solution / 0.3% (w/v) (as netilmicin sulfate) and 0.1% (w/v) dexamethasone (as dexamethasone sodium phosphate)	Disodium phosphate dodecahydrate, monobasic sodium phosphate, purified water, sodium citrate. Preservative free.

NETILDEX is a clear, colorless slightly viscous solution. Each ml contains: netilmicin sulfate 4.55 mg (equivalent to netilmicin 3 mg) and dexamethasone sodium phosphate 1.32 mg (equivalent to dexamethasone 1 mg).

Ophthalmic solution with preservative
NETILDEX is available as a sterile ophthalmic solution with preservative in individual 5 mL plastic bottles.

Preservative-free ophthalmic solution

NETILDEX is available as a preservative-free sterile ophthalmic solution in 0.3 mL plastic containers wrapped in an aluminum pouch containing 5 preservative-free containers and are available in 15 or 20 pack sizes.

6 WARNINGS AND PRECAUTIONS

General

FOR TOPICAL OPHTHALMIC USE ONLY.
NOT FOR INJECTION INTO THE EYE. NOT FOR OTIC USE. NOT FOR NASAL USE. NOT FOR ORAL INGESTION.

The safety and efficacy of NETILDEX therapy for a duration beyond 7 days have not been established.

Drug interactions are known to occur with topical ophthalmic and/or systemic exposure to corticosteroids and aminoglycosides. Serious adverse reactions, and increased risk of adverse reactions, may occur with sequential or concurrent use of interacting drugs, including additional corticosteroids and/or aminoglycosides (see **DRUG INTERACTIONS**).

Carcinogenesis and Mutagenesis

Refer to Non-Clinical Toxicology section.

Driving and Operating Machinery

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

Endocrine and Metabolism

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 and patients treated with inhibitors of cytochrome P450 3A4 such as ritonavir (see **DRUG INTERACTIONS**). In these cases, treatment should not be discontinued abruptly, but progressively tapered.

Immune

Sensitivity to topically applied aminoglycosides or corticosteroids 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 bulbous reactions. If hypersensitivity develops during use of NETILDEX, treatment should be discontinued.

Cross-hypersensitivity to other aminoglycosides and to other corticosteroids can occur. Patients who become sensitized to topical netilmicin or to topical dexamethasone may also be sensitive to other topical and/or systemic aminoglycosides or corticosteroids.

Monitoring and Laboratory Tests

Ophthalmic evaluation and intraocular pressure (IOP) should be routinely and frequently monitored according to current clinical practice recommendations.

Ophthalmic examinations are recommended during prolonged therapy.

In predisposed patients, consideration should be given to assessment of auditory function, hypothalamic-pituitary-adrenal (HPA) axis function, or renal function, as appropriate.

Ophthalmologic

Increased risk of bleb formation, cataract, glaucoma, impaired healing, infection, IOP increase, perforation and central serous chorioretinopathy (CSCR) have been associated with the use of topical corticosteroids.

Prolonged or intensive use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. This risk is higher in patients with diabetes. In patients with diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical corticosteroids.

Corticosteroids should not be used in the presence of glaucoma, ocular hypertension (IOP ≥ 24 mmHg) or a history of steroid-induced IOP elevation unless absolutely necessary and under close ophthalmologic monitoring. Caution should be exercised, and duration of treatment should be kept as short as possible.
If a patient presents with symptoms such as blurred vision or other visual disturbances, consider referral to an ophthalmologist for evaluation.

Impaired Healing

Topical ophthalmic corticosteroids may slow corneal wound healing. Concurrent use of topical ophthalmic corticosteroids and topical NSAIDs may increase the potential for, and severity of, healing problems (see **DRUG INTERACTIONS**).

Bleb Formation

Topical ophthalmic corticosteroids may increase the incidence of bleb formation after cataract surgery.

Infections

Prolonged use of corticosteroids may suppress the host response, and aid in the establishment of secondary ocular bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection. In patients with a history of herpetic infection of the cornea, reactivation of the disease may occur with use of topical ophthalmic corticosteroids.

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application; fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. If fungal infection occurs, corticosteroid therapy, including NETILDEX, should be discontinued and appropriate therapy initiated.

NETILDEX, if handled incorrectly, can become contaminated, which may lead to eye infections. Serious ocular damage and subsequent loss of vision may result from using contaminated eye drops. Advise patients not to touch the tip of the container to any surface including the eye to avoid possible contamination.

Corneal Deposits

NETILDEX contains phosphates which may lead to corneal deposits or corneal opacity when topically administered. Risk factors include pre-existing corneal damage. NETILDEX should be used with caution in patients presenting with compromised cornea and in instances where the patient is receiving other phosphate containing eye medications. If significant clinical improvement does not occur within a few days, or if any irritation or sensitization phenomena occur, discontinue NETILDEX and initiate appropriate therapy.

Benzalkonium Chloride

NETILDEX ophthalmic solution with preservative contains the preservative benzalkonium chloride, which may cause eye irritation and is known to bind to, and discolour, soft contact lenses.

Use of Contact Lenses

Contact lens wear is not recommended during treatment with NETILDEX due to the increased risk of ocular infection and irritation. If contact lens wear is necessary, it is advised to use NETILDEX preservative-free. Avoid contact of NETILDEX with preservative with soft contact lenses due to the presence of the preservative benzalkonium chloride.

Sexual Health

Studies have not been performed to evaluate the effect of topical ophthalmic administration of NETILDEX on human fertility.

Susceptibility / Resistance

Development of Drug Resistant Bacteria

Prescribing NETILDEX in the absence of the authorized indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth

Prolonged use of antibacterials such as netilmicin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection or drug resistance occurs, discontinue NETILDEX and initiate appropriate therapy.

6.1 Special Populations

6.2 Pregnant Women

There are no adequate and well-controlled studies with NETILDEX in pregnant women.

NETILDEX should be given to a pregnant woman only if the potential benefit to the mother outweighs the potential risk to the fetus. 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 dexamethasone and netilmicin (see **TOXICOLOGY**).
Netilmicin does cross the placenta into the fetus after intravenous dosing in pregnant women. Netilmicin is not expected to cause ototoxicity from *in utero* exposure. Prolonged or repeated corticosteroid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation.

6.3 Breast-feeding

It is not known whether topical NETILDEX therapy results in netilmicin or dexamethasone excretion in human milk. Netilmicin is excreted in human milk after systemic absorption. No data is available on the passage of dexamethasone into human breast milk, but the molecular weight of dexamethasone is small enough to allow for transfer. Systemic corticosteroids could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

Because many drugs are excreted in human milk, a decision should be made either to discontinue breast-feeding or discontinue/abstain from NETILDEX therapy, taking into account the importance of NETILDEX therapy to the mother and the potential risk to the infant.

6.4 Pediatrics

Pediatrics (< 18 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Significant adrenal suppression has been documented in infants on ophthalmic dexamethasone to control inflammation following cataract surgery. Monitor infants for adrenal suppression; and use low doses of ophthalmic corticosteroids for the shortest duration possible.

Pediatric patients are at a greater risk for corticosteroid-induced ocular hypertension, and it may occur earlier in children than in adults. Pediatric patients are also at a greater risk for developing Cushing's syndrome and/or adrenal suppression associated with intensive or long-term continuous therapy with dexamethasone.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component or the combination.

The following serious adverse reactions occurred in 0.5% (4/751) of clinical trial subjects treated with NETILDEX (or concurrent single actives), following cataract surgery: bacterial conjunctivitis, corneal oedema, endophthalmitis and uveitis.

Symptoms of ocular discomfort (pain, photophobia, tearing, burning, stinging, itching, blurred vision) were common on the day following cataract surgery, and most resolved within 7 days

treatment. In approximately 18% (71/395) of clinical trial subjects treated with NETILDEX, symptoms of ocular discomfort worsened; and in 2.3% (8/395), symptoms worsened to severe.

Intraocular pressure at days 7 or 14 post-cataract surgery, increased from pre-surgery baseline by ≥ 10 mmHg in 0.15% (1/638) of patients, and by 6 to < 10 mmHg in 0.6% (4/638) of patients.

Cases of corneal deposits or corneal opacity have been reported in association with the use of phosphate containing eye drops.

Aminoglycosides

Serious adverse reactions which have been reported in patients receiving systemic aminoglycoside therapy, some with netilmicin, include: ototoxicity, nephrotoxicity, eighth cranial nerve toxicity, neuromuscular blockade, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Risk factors include: pre-existing renal, vestibular or auditory impairment; concurrent or sequential therapy with nephrotoxic or ototoxic agents; prolonged therapy; high dose; drug interactions.

Corticosteroids

Other reactions which have been reported after use of systemic and topical corticosteroids include: altered vision (visual disturbances, defects in visual acuity and visual fields, loss of accommodation), cataract (posterior subcapsular), central serous chorioretinopathy (CSCR), corneal perforation, Cushing's syndrome/ adrenal suppression, dysregulation (glucose, potassium), impaired healing, infections (secondary, fungal, viral, worsening Herpes simplex infection), mydriasis, and decreased response to somatotropin. Risk factors include prolonged or intensive corticosteroid use; diabetes; corneal or scleral thinning; concurrent use of topical nonsteroidal anti-inflammatory drugs (NSAIDs); pediatrics; hepatic impairment, hypoprothrombinemia, or hypothyroidism.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of NETILDEX and netilmicin sulfate (with or without concurrent dexamethasone sodium phosphate), formulated as topical eye solution, eye gel or eye ointment was evaluated across 13 prospective, randomized trials for a treatment period of 6 to 14 days, and followed post-treatment up to study day 14 and 30, respectively, in a total of 1228 adult subjects. Formulation strengths were 0.3% netilmicin (as netilmicin sulfate) and/or 0.1% dexamethasone (as dexamethasone sodium phosphate). Among these trials were 751 unique patients from 4 trials in a post-phacoemulsification cataract surgery / intraocular lens implantation setting (580 treated with NETILDEX solution; 171 treated with concurrent single actives); 50 patients from 1 trial in a post-vitreoretinal surgery setting treated with NETILDEX solution; 334 patients from 6 trials in a non-surgical, conjunctivitis setting (71 treated with NETILDEX solution; 150 treated with netilmicin solution and netilmicin ointment; 122 treated with netilmicin solution) and 84 healthy subjects from 2 trials (21 treated with NETILDEX solution; 21 treated with NETILDEX gel; 21 treated with netilmicin solution; 21 treated with netilmicin gel). Subjects were treated with one drop/eye four times per day, except for 42 healthy subjects who were treated six times per day. Subjects treated with netilmicin ointment received it at bedtime as one of the four daily treatments. The safety

analyses were conducted on available data from the safety population, which included all randomized subjects who received at least 1 dose of investigational treatment.

In these trials, 425 adult subjects were treated with active comparators. Among these were 155 patients from 2 trials in a post-phacoemulsification cataract surgery / intraocular lens implantation setting (75 treated with 0.3% tobramycin and 0.1% dexamethasone fixed dose combination ophthalmic suspension; 80 treated with 0.2% betamethasone and 0.5% chloramphenicol fixed dose combination eye drops); 53 patients from 1 trial in a post-vitreoretinal surgery setting treated with 0.3% tobramycin and 0.1% dexamethasone fixed dose combination ophthalmic suspension; 217 patients from 3 trials in a non-surgical, conjunctivitis setting (68 treated with 0.3% tobramycin and 0.1% dexamethasone fixed dose combination ophthalmic suspension; 46 treated with 0.4% chloramphenicol, 0.5% rolitetracycline and 18 000 000/ 100 ml I.U. colistin fixed dose combination eye drops and ointment; 103 treated with 0.3% gentamicin drop and 0.3% gentamicin ointment).

Post-operative inflammation following cataract surgery

Table 2 summarizes treatment-emergent adverse events from four trials of patients treated for post-operative inflammation following uncomplicated phacoemulsification / intraocular lens implantation cataract surgery. Trial subjects were Caucasian male and female adults (age range 40 to 94 years, evenly distributed to age categories ≤ 65; 66 to 74; and ≥75 years), and without: histories of ocular inflammatory or infectious diseases or syndromes, ocular pathology; intraocular pressure > 24 mmHg; ocular surgery in the affected eye within 12 months; laser treatment in the affected eye within 6 months; known or suspected relevant allergy; treatment for an external ocular infection within 1 month; anti-inflammatory therapy within 30 days; antibacterial therapy within 15 days; use of ocular medication other than artificial tears; pregnancy or nursing. Concurrent systemic antibacterial therapy was received during the study period, starting one day before or after surgery, by 35% of patients treated with NETILDEX (or concurrent single actives), and by 43% of patients treated with active comparators. Data on the use of other concurrent medications were not available to Health Canada.

Additional adverse events reported in other trials of subjects treated with NETILDEX or ophthalmic netilmicin (with or without concurrent dexamethasone sodium phosphate) are listed following Table 2.

Ocular Discomfort

In the four cataract surgery / intraocular lens implantation trials, patients were scored none, mild, moderate or severe for six ocular discomfort symptoms (pain, photophobia, tearing, burning, stinging and blurred vision (two studies) or itching (two studies)) at days 1, 7 and 14 post-surgery. The overall incidence of patients who experienced a symptom on day 1 post-surgery was similar for NETILDEX (or concurrent single actives) and active comparators, ranging from approximately 17% to 37% across the symptoms. Based on data available from two of the four studies, one or more worsened ocular symptoms during the 14-day study period (7 days treatment, 7 days follow-up) were experienced by 21% (83/395) patients treated with NETILDEX (or concurrent single actives) and by 12% (9/75) of patients treated with active comparator (0.3% tobramycin and 0.1% dexamethasone fixed dose combination ophthalmic suspension); among these, 3% (12/395) and 8% (6/75), respectively, were transient with improvement by day 14. Symptoms worsened to severe in 2.3% (8/395) and 1.3% (1/75) of patients treated with NETILDEX and active comparator, respectively. Overall treatment group mean symptom scores improved over the study period similarly for the NETILDEX (or concurrent single actives) and the active comparator groups.

Table 2 – Clinical Trial Treatment-Emergent Adverse Events[a] Reported by at least one Subject in Patients Following Cataract Surgery

System Organ Class MedDRA Preferred Term	NETILDEX or concurrent single actives[b] N=751 n (%)	Active Comparator N=155 n (%)
Ear and labyrinth disorders		
Vertigo	1 (0.1)	0 (0.0)
Eye disorders		
Ocular infections, irritations and inflammations	15 (2.0)	0 (0.0)
Conjunctivitis	4 (0.5)	0 (0.0)
Conjunctivitis allergic	3 (0.4)	0 (0.0)
Conjunctivitis bacterial	1 (0.1)	0 (0.0)
Corneal edema	3 (0.4)	0 (0.0)
Cystoid macular edema	1 (0.1)	0 (0.0)
Endophthalmitis	1 (0.1)	0 (0.0)
Macular edema	1 (0.1)	0 (0.0)
Uveitis	1 (0.1)	0 (0.0)
Retina, choroid, and vitreous haemorrhages and vascular disorders	2 (0.3)	0 (0.0)
Conjunctival haemorrhage	1 (0.1)	0 (0.0)
Retinal haemorrhage	1 (0.1)	0 (0.0)
Hepatobiliary disorders		
Coma hepatic	1 (0.1)	0 (0.0)
Investigations		
Intraocular pressure increased[c]	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications		
Humerus fracture	1 (0.1)	0 (0.0)
Lower limb fracture	1 (0.1)	0 (0.0)
Post-operative wound complication	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorder		
Back pain	1 (0.1)	0 (0.0)
Psychiatric Disorders		
Anxiety	1 (0.1)	0 (0.0)
Vascular Disorders		
Hypotension	1 (0.1)	0 (0.0)
Peripheral ischemia	1 (0.1)	0 (0.0)

[a] Adverse events regardless of causality, excluding the ocular discomfort symptoms of pain, photophabia, tearing burning, stinging, itching, blurred vision.
[b] 0.3% netilmicin (as netilmicin sulfate) and 0.1% dexamethasone (as dexamethasone sodium phosphate)
[c] "Intraocular pressure increased" was defined as an increase ≥ 10 mmHg from pre-surgery baseline.

Additional Adverse Events from Other Clinical Trials

Additional adverse events reported in other trials of subjects treated with NETILDEX (or ophthalmic netilmicin sulfate with or without concurrent dexamethasone sodium phosphate) were: conjunctival oedema, corneal pigmentation, eye discharge, epistaxis, erythema of eyelid, eyelid oedema, headache, ocular hyperaemia.

7.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Intraocular Pressure

Intraocular pressure (IOP) data was available from four of the five post-surgical trials. IOP was monitored in both eyes at pre-surgery, and post-surgery on days 7 and 14, as well as on day 30 in one trial, by applanation tonometry. NETILDEX (or concurrent single actives) and active comparator (0.3% tobramycin and 0.1% dexamethasone fixed dose combination ophthalmic suspension) treatment group mean IOPs were similar at all of the time points. Table 3 summarizes the incidences of IOP categorical increases compared to pre-surgery baseline. One subject treated with NETILDEX developed a clinically significant IOP increase (both an IOP increase of ≥ 10 mmHg and an absolute IOP of ≥ 21 mmHg) detected at day 7 and was treated for glaucoma for 24 days with additional 1% brinzolamide.

Table 3 - Incidence of Categorical IOP Increases from Pre-surgery Baseline

Clinical Setting	IOP Increase			
	NETILDEX (or concurrent single actives) n/N (%)		Active Comparator n/N (%)	
Studies in post-surgery trials	6 to < 10 mmHg 4/638 (0.63)	≥10 mmHg 1/638 (0.16)	6 to < 10 mmHg 1/126 (0.8)	≥ 10 mmHg none

7.4 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable.

7.5 Post-Market Adverse Reactions

The following additional adverse reactions were identified through post-market surveillance.

Cardiovascular: sinus bradycardia.

Ear and Labyrinth Disorders: ear pruritus.

Eye: abnormal sensation in eye, chorioretinopathy, conjunctival hyperaemia, eye oedema, eye swelling, eyelid ptosis, foreign body sensation in eye, halo vision, keratitis bacterial, punctate keratitis, visual acuity reduced.

Endocrine Disorders: adrenal suppression.

Gastrointestinal Disorders: nausea, oral discomfort, palatal oedema, vomiting.

General Disorders and Administration Site Conditions: drug ineffective, drug interaction.

I**mmune System Disorders:** hypersensitivity.

Investigations: international normalized ratio increased.

Metabolism and Nutrition Disorders: Cushing's syndrome, hyperkalemia.

Nervous System Disorders: ageusia, disgeusia, dizziness, hypoglycemic unconsciousness.

Psychiatric disorders: insomnia, nervousness.

Renal and Urinary Disorders: chronic kidney disease.

Skin and Subcutaneous Disorders: eczema, lip oedema, swelling face, pruritus.

8 DRUG INTERACTIONS

8.1 Overview

No specific drug interaction studies have been performed with NETILDEX.

There is a risk of additive toxicity with combined topical and systemic use. In order to prevent additive toxicity, avoid combined use (and sequential use in some cases) with any agent that is known to impair healing; increase intraocular pressure; contain phosphates for ophthalmic use; to inhibit cytochrome P450 3A4; or to be nephrotoxic, ototoxic or neurotoxic. If combined use cannot be avoided, ophthalmic evaluation and monitoring of IOP, total serum aminoglycoside concentration, renal function and/or auditory function are recommended, as appropriate. Refer to the prescribing information of the systemic drug product.

Benzalkonium chloride binds to soft contact lenses which can lead to ocular irritation, and which can cause contact lens discoloration.

8.2 Drug-Drug Interactions

Table 4 - Established or Potential Drug-Drug Interactions, NETILDEX

Interacting Drugs	Source of Evidence	Effect	Clinical Comment
Dexamethasone sodium phosphate			
Topical nonsteroidal anti-inflammatory drugs (NSAIDs)	L	Impaired healing	Increased risk and/or increased severity may occur. Avoid concurrent use. If concurrent use cannot be avoided, monitor the patient closely.
Topical steroids	L	Increased IOP; Impaired healing	Increased risk and/or increased severity may occur. Avoid concurrent use. If concurrent use cannot be avoided, monitor the patient closely.
Anticholinergics, especially atropine and related compounds	L	Increased IOP	Increased risk of increased IOP is associated with prolonged corticosteroid therapy in patients predisposed to acute angle closure. Avoid concurrent use. If concurrent use cannot be avoided, monitor the patient closely.
Cytochrome P450 3A4 (CYP3A4) inhibitors (including ritonavir)	L	Increased dexamethasone systemic exposure; adrenal suppression; Cushing's syndrome	Increased risk of effects, including adrenal suppression/Cushing's syndrome. Avoid concurrent use, unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects. In case of adrenal suppression / Cushing's syndrome, treatment should not be discontinued abruptly, but progressively tapered.
Systemic corticosteroids	L	Additive effects and toxicities	Avoid concurrent use. If concurrent use cannot be avoided, refer to the prescribing information of the systemic drug product.

Interacting Drugs	Source of Evidence	Effect	Clinical Comment
Phosphates			
Phosphate containing eye therapies	L	Corneal deposits or corneal opacity	Increased risk. Avoid concurrent use. If concurrent use cannot be avoided, monitor the patient closely.
Netilmicin sulfate			
Systemic or topical drugs with nephrotoxic potential: aminoglycosides, anticholinergics (atropine), cephalosporins (cephaloridine), colistin, cisplatin, diuretics (ethacrynic acid, furosemide), polymyxin B, streptomycin, vancomycin, viomycin	L	Additive toxicity	Increased risk with concurrent or sequential use. Avoid concurrent or sequential use. If concurrent or sequential use cannot be avoided, refer to the prescribing information of the systemic drug product. For aminoglycosides, monitor the total serum aminoglycoside concentration.
Systemic or topical drugs with ototoxic potential: aminoglycosides, loop diuretics	L	Additive toxicity	Increased risk with concurrent or sequential use. Avoid concurrent or sequential use. If concurrent or sequential use cannot be avoided, refer to the prescribing information of the systemic drug product. For aminoglycosides, monitor the total serum aminoglycoside concentration.
Systemic, topical or local drugs with neurotoxic potential: aminoglycosides, botulinum toxin type A, succinylcholine, tubocurarine	L, T	Additive toxicity; potentiated interference with neuromuscular transmission	Concurrent use may increase the risk of eighth cranial nerve toxicity or neuromuscular blockade. Avoid concurrent use. If concurrent use cannot be avoided, refer to the prescribing information of the systemic drug product. Caution should be exercised when therapy using botulinum toxin type A is used with aminoglycosides.
Beta-lactam	T	Antagonism	In vitro, the combination of an aminoglycoside with a beta-lactam (penicillin or cephalosporin) may result in a significant mutual inactivation.

Legend: L = literature; T = Theoretical

8.3 Drug-Food Interactions

Interactions with food have not been established.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

8.6 Drug-Lifestyle Interactions

Interactions with alcohol have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Dexamethasone, a corticosteroid, suppresses the inflammatory response.

Netilmicin is an aminoglycoside antibacterial, which accomplishes its primary effect on bacterial cells by inhibiting the normal protein synthesis in susceptible bacteria.

9.2 Pharmacodynamics

Dexamethasone

Dexamethasone is a synthetic corticosteroid. Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules, cyclooxygenase I or II (COX-I or II), and cytokine expression. This results 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 tissues.

Netilmicin

Netilmicin is a semi-synthetic aminoglycoside antibiotic. It is active *in vitro* against most Gram-negative micro-organisms and against many Gram-positive organisms, including Staphylococcus aureus.

9.3 Pharmacokinetics

Absorption

Dexamethasone

As a class, these agents are readily delivered to the cornea, and readily absorbed into the eye from a variety of topical routes (e.g., eyedrops, subconjunctival injection, etc.). When applied as an ophthalmic solution or suspension to the cornea, dexamethasone is readily absorbed. Peak concentrations of dexamethasone are observed in humans between 90 and 120 minutes after administration and measurable quantities have been detected in the aqueous humor up to 12 hours after instillation.

Netilmicin

As with all aminoglycosides, netilmicin is scarcely lipophilic, therefore, after topical administration, it poorly penetrates the anterior chamber of the eye.

Distribution

Dexamethasone

In humans, systemic absorption of topically applied dexamethasone is low.

Netilmicin

In human, netilmicin concentration in tears decreases after a first order kinetics, showing concentrations of netilmicin on the ocular surface more than 120 minutes after eye drop instillation.

Metabolism and Elimination

Dexamethasone

After administration, dexamethasone sodium phosphate is subjected to a hydrolysis reaction, catalyzed by enzymes in the tear film and cornea, and is partly converted into the lipid-soluble dexamethasone alcohol. Following systemic exposure, dexamethasone is excreted in urine practically unchanged.

Netilmicin

Netilmicin, as well as other aminoglycoside antibiotics, is primarily eliminated unchanged by the kidney.

Special Populations and Conditions

Pediatrics: (< 18 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **WARNNGS AND PRECAUTIONS**).

10 STORAGE, STABILITY AND DISPOSAL

NETILDEX with preservative and preservative-free formulations: Store between 15-30°C and in the original package (including outer carton to protect from light when not in use).

NETILDEX ophthalmic solution with preservative: The multi-use container and any unused content must be discarded 28 days after first opening.

NETILDEX preservative-free ophthalmic solution: The single-use container and any unused content must be discarded after administration.

11 SPECIAL HANDLING INSTRUCTIONS

Keep out of the reach and sight of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

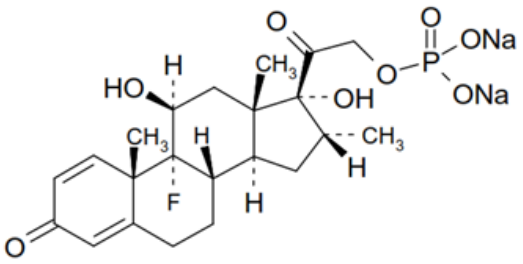
Drug Substance: Dexamethasone sodium phosphate

Proper name: Dexamethasone sodium phosphate

Chemical name: 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate

Molecular formula and molecular mass: $C_{22}H_{28}FNa_2O_8P$; 516.4

Structural formula:



Physicochemical properties: Dexamethasone sodium phosphate is a white or almost white powder, very hygroscopic, freely soluble in water, slightly soluble in alcohol, practically insoluble in ether and in methylene chloride.

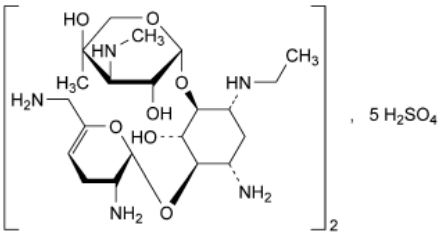
Drug Substance: Netilmicin sulfate

Proper name: Netilmicin sulphate

Chemical name: 2-Deoxy-6-*O*-[3-deoxy-4-C-methyl-3-(methylamino)-β -*L*-arabinopyranosyl]-4-*O*-(2,6diamino-2,3,4,6-tetradeoxy-α -*D-glycero*-hex-4-enopyranosyl)-1-N-ethyl-D-streptamine, sulfate

Molecular formula and molecular mass: $C_{42}H_{92}N_{10}O_{34}S_5$; 1442

Structural formula:



Physicochemical properties: Netilmicin sulfate is a white or yellowish-white crystalline powder, very hygroscopic, very soluble in water, practically insoluble in acetone and in alcohol.

13 CLINICAL TRIALS

13.1 Efficacy and Safety Studies

Tables 5, 6 and 7 summarize the main study in support of the efficacy and safety of NETILDEX (netilmicin and dexamethasone ophthalmic solution).

Trial Design and Study Demographics
Table 5 - Summary of patient demographics for clinical trials

Study # Trial design	Treatment Groups	Dosage, route of administration and duration	Study Subjects (N) (Enrolled / Full Analysis / Per Protocol)	Mean age (Range)	Study Subjects by Sex (N)
014 Randomized (2:1 allocation ratio), double-masked, active-control, single-center	NETILDEX ophthalmic solution with preservative	one eye-drop in the conjunctival sac of the operated eye immediately after surgery, before bandaging; then one drop/operated eye four times per day for 7±1 days from post-surgery day 1 to day 7±1	148 / 135 / 132	70.0 (41-91)	70 M / 78 F
	Active Comparator 0.3% tobramycin and 0.1% dexamethasone ophthalmic suspension fixed dose combination (TOBRADEX)		75 / 73 / 71	69.1 (40-90)	40 M / 35 F

Study 014

The main goal of study 014 was to assess the anti-inflammatory proprieties of NETILDEX in the treatment of post-cataract surgery ocular inflammation. Trial subjects were unique Caucasian male and female adult patients with mild to moderate ocular inflammation, based on scores for anterior chamber flare and cells, following unilateral uncomplicated phacoemulsification cataract extraction and intraocular lens implantation surgery. Subject age was approximately evenly distributed across age categories ≤ 65, 66 to 74 and ≥ 75 years.

At enrollment subjects were without: histories of ocular inflammatory or infectious diseases or syndromes, concurrent ocular pathologies; intraocular pressure > 24 mmHg; ocular surgery in the affected eye within 12 months; laser treatment in the affected eye within 6 months; known or suspected relevant allergy; treatment for an external ocular infection within 1 month; anti-inflammatory therapy within 30 days; antibacterial therapy within 15 days; use of ocular medication other than artificial tears; pregnancy or nursing.

Systemic antibacterial therapy, starting on the day of surgery or one day before, was received by 58/148 (39%) of subjects treated with NETILDEX, and by 32/75 (43%) of subjects treated with active comparator. No subject received intra-operative antibacterial therapy. Data on the use of other concurrent medications were not available to Health Canada.

The primary efficacy parameters and endpoint were anterior chamber flare and cells at end of treatment on post-surgery day 7±1. Anterior chamber flare and cells were evaluated in the operated eye by slit-lamp examination (biomicroscopy) post-surgery on days 1, 7±1, and 14±2 (follow-up visit). Anterior chamber flare was scored 0 (none); 1 (mild, barely detectable); 2 (moderate, iris and lens details clear) and 3 (severe, iris and lens details not visible and fibrin in anterior chamber). Anterior chamber cells were scored 0 (none); 1 (mild, 1 to 10 cells); 2 (moderate, 11 to 50 cells); 3 (severe > 50 cells).

Key secondary efficacy parameters were the ocular discomfort parameters pain, photophobia and tearing.

13.2 Study Results

Efficacy Results are summarized in Tables 6 and 7.

Table 6 - Frequency for Slit-Lamp Examination Data – Full Analysis Population

	Day 1 post-surgery				Day 7 ± 1 day post surgery				Day 14 ± 2 days post surgery			
	Netildex		Comparator		Netildex		Comparator		Netildex		Comparator	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Number of patients	**135**	**(64.9)**	**73**	**(35.1)**	**135**	**(64.9)**	**73**	**(35.1)**	**135**	**(64.9)**	**73**	**(35.1)**
Anterior chamber flare												
None	2	(1.5)	2	(2.7)	105	(77.8)	50	(68.5)	130	(96.3)	71	(97.3)
Mild	121	(89.6)	59	(80.8)	28	(20.7)	23	(31.5)	5	(3.7)	2	(2.7)
Moderate	12	(8.9)	11	(15.1)	2	(1.50)	0	(0.0)	0	(0.0)	0	(0.0)
Severe	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Anterior chamber cells												
None	2	(1.5)	2	(2.7)	105	(77.8)	50	(68.5)	130	(96.3)	71	(97.3)
Mild	123	(91.1)	58	(79.5)	28	(20.7)	23	(31.5)	4	(3.0)	2	(2.7)
Moderate	10	(7.4)	12	(16.4)	2	(1.5)	0	(0.0)	1	(0.7)	0	(0.0)
Severe	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 7- Frequency of Ocular Discomfort Parameter Data (Pain, Photophobia, Tearing)– Full Analysis Population

	Day 1 post-surgery				Day 7 ± 1 day post surgery				Day 14 ± 2 days post surgery			
	Netildex		Comparator		Netildex		Comparator		Netildex		Comparator	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Number of patients	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**
Pain												
None	121	(89.6)	58	(76.5)	133	(98.5)	69	(94.5)	134	(99.3)	73	(100.0)
Mild	14	(10.4)	14	(19.2)	2	(1.5)	3	(4.1)	1	(0.7)	0	(0.0)
Moderate	0	(0.0)	1	(1.4)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Severe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	Day 1 post-surgery				Day 7 ± 1 day post surgery				Day 14 ± 2 days post surgery			
	Netildex		Comparator		Netildex		Comparator		Netildex		Comparator	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Number of patients	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**	**135**	**(64.9)**
Photophobia												
None	123	(91.1)	65	(89.0)	134	(99.3)	71	(97.3)	134	(99.3)	73	(100.0)
Mild	9	(6.7)	6	(8.2)	1	(0.7)	1	(1.4)	1	(0.7)	0	(0.0)
Moderate	3	(2.2)	2	(2.7)	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Severe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tearing												
None	114	(84.4)	59	(80.8)	129	(95.6)	68	(93.2)	133	(98.5)	70	(95.9)
Mild	19	(14.1)	12	(16.4)	6	(4.4)	4	(5.5)	1	(0.7)	3	(4.1)
Moderate	2	(1.5)	2	(2.7)	0	(0.0)	1	(1.4)	1	(0.7)	0	(0.0)
Severe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

14 MICROBIOLOGY

Netilmicin has been shown to be active *in vitro* against susceptible Gram positive and negative bacterial strains. It does not have any activity against anaerobes. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) contains MIC distribution data for netilmicin and sets the epidemiological breakpoint (ECOFF). The relationship between systemic clinical breakpoints and clinical topical efficacy is not established. Bacterial resistance patterns may be regional.

Table 8 - MIC Breakpoints for Netilmicin

Microorganism	Clinical MIC breakpoints (mg/l)		
	S (≤)	R (≥)	ECOFF
Enterobacteriaceae	2	4	2
Pseudomonas	4	4	4
Acinetobacter	4	4	NR
Staphylococcus	1	1	1
Staphylococcus, coagulase negative	1	1	NR

Notes: S= Sensitive. R = Resistant.

ECOFF = Common epidemiological cut-off value for surveillance of resistance

NR = Not reported.

15 NON-CLINICAL TOXICOLOGY

General toxicology

Tolerability to eye drops containing a fixed combination of 0.1% dexamethasone and 0.3% netilmicin, following repeated ocular administration, was investigated in rabbit over a period of 28 days. No lesions at the conjunctival and corneal level or of the fundus were observed and ocular reflexes were not affected. Analysis of organ weight data revealed a number of significant differences between animals treated with the test item compared to the controls treated with placebo.

Single-dose animal studies with dexamethasone observe body weight reduction. A high single dose of aminoglycosides causes respiratory paralysis and death in rats and mice.

Carcinogenicity

No studies were conducted.

Genotoxicity

No genotoxicity studies were conducted with NETILDEX.

Analyses of chromosomal aberrations, sister-chromatid exchanges (SCEs) in human lymphocytes and micronuclei and SCEs in mouse bone marrow showed dexamethasone to be capable of attacking the genetic material. However, the Ames/Salmonella assay, both with and without S9 mix, did not show any increase in His+ revertants.

Netilmicin was examined for mutagenic and DNA-modifying activity in a series of *in vitro* microbial assays employing Salmonella and Escherichia indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. The doses ranged between 0.5 µg and 5000 µg per plate. Netilmicin did not demonstrate DNA-modifying or genetic activity in any of the assays conducted in this evaluation and was considered not mutagenic or genotoxic under these test conditions.

Reproductive and Developmental Toxicology

Corticosteroids have been shown to be teratogenic in animal studies. Dexamethasone animal studies resulted in reproductive and developmental abnormalities, including fetal abortions, cleft palate, CNS effects, brain defects, and heart defects following high dose systemic administration. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy.

Fertility, teratogenicity and postnatal studies of netilmicin in rats and rabbits have not provided any significant evidence of toxicity of netilmicin, particularly following ocular administration.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrNETILDEX®
Netilmicin and Dexamethasone Ophthalmic Solution with Preservative

Read this carefully before you start taking **NETILDEX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NETILDEX**.

What is NETILDEX used for?

NETILDEX is used to reduce inflammation of the eye following cataract surgery. It is also used to reduce the risk of bacterial infection.

Antibacterial drugs like NETILDEX treat only bacterial infections. They do not treat viral infections.

How does NETILDEX work?

NETILDEX contains:
- Dexamethasone sodium phosphate: a corticosteroid that reduces inflammation.
- Netilmicin sulfate: an aminoglycoside antibiotic which kills bacteria.

Together, they treat the eye.

What are the ingredients in NETILDEX?

Ophthalmic solution with preservative:

Medicinal ingredients: 0.3% w/v netilmicin (as netilmicin sulfate) and 0.1% w/v dexamethasone (as dexamethasone sodium phosphate).

Non-medicinal ingredients:
Preservative: benzalkonium chloride 0.005%.
Others: disodium phosphate dodecahydrate, sodium citrate, monobasic sodium phosphate and purified water.

NETILDEX comes in the following dosage forms:

NETILDEX ophthalmic solution with preservative:

One bottle containing 5 ml of NETILDEX ophthalmic solution packed in a carton.

NETILDEX preservative-free ophthalmic solution:

Five preservative-free containers of 0.3 ml of NETILDEX ophthalmic solution wrapped in an aluminium pouch (flow-pack). Three or four flow-packs (which is the equivalent of 15 or 20 preservative-free containers) are packed in a carton.

Do not use NETILDEX if you:

- Are allergic (*hypersensitive*) to netilmicin, or other aminoglycosides, dexamethasone or other corticosteroids or any of the other ingredients in NETILDEX solution (see **What are the ingredients in NETILDEX?**).
- Have smallpox, chickenpox or any other viral infection of the eye.

- Have inflammation of the eye that is caused by a viral infection (herpes simplex keratitis or other herpes simplex eye infections).
- Have a fungal or parasitic infection of the eye.
- Have a mycobacterial infection of the eye, including tuberculosis.
- Have an active untreated eye infection.
- Recently had a simple removal of an object from the eye.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NETILDEX. Talk about any health conditions or problems you may have, including if you:

- Were advised by your healthcare provider that the pressure in your eye is too high (glaucoma).
- Have used other corticosteroids before in the past.
- Develop an allergic reaction. Signs may include skin redness, itching and rash. You should stop taking NETILDEX.
- Are taking another aminoglycoside antibiotic.
- Have diabetes. You may be at a higher risk of developing increased pressure in the eyes, vision problems or cataracts.
- Have a disease-causing thinning of your cornea (the front part of the eye) or sclera (white part of the eye). Small tears (*perforations*) have occurred.
- Have had damage to your cornea (the front part of the eye).
- Have recently had surgery on your eye. NETILDEX may cause blisters on your eye or delayed healing.
- Wear contact lenses. Contact lens wear is not recommended during treatment of eye inflammation or eye infection.
- Are pregnant, may be pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed.
- Are under 18 years of age. NETILDEX has not been tested in children under 18 years of age.

Other warnings you should know about:

Taking NETILDEX for a long time increases the risk of developing:

- High eye pressure.
- Vision problems.
- Cataracts.
- An eye infection.
- Problems with your metabolism.

Your doctor should check your eye pressure regularly.

You may experience temporary blurred vision after taking NETILDEX. Do not drive or operate machinery until your vision has returned to normal.

NETILDEX contains the preservative benzalkonium chloride. Benzalkonium chloride discolours soft contact lenses and may cause eye irritation. If you must wear contact lenses, remove them before applying NETILDEX, wait at least 15 minutes before putting your lenses back in. If you wear soft contact lenses, it is advised that you use NETILDEX in preservative-free containers since it does not contain preservative.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drug interaction studies have not been done with NETILDEX.

The following may interact with NETILDEX:

- Any other antibiotics, in particular: aminoglycosides, penicillin, cephalosporin, polymyxin B, colistin, viomycin, streptomycin, vancomycin and cephaloridine;
- Cisplatin, an anti-cancer drug;
- Diuretics (medicines to reduce water retention) such as ethacrynic acid and furosemide;
- Anticholinergic medicines (medicines that stop glands secreting), such as atropine;
- Ritonavir (medicines used to treat HIV);
- Other medicines containing phosphates. Your doctor will check the cornea at regular intervals;
- Nonsteroidal anti-inflammatory drugs (NSAIDs);
- Botulinum toxin Type A, used to treat spasms, severe underarm sweat;
- Muscle relaxants, in particular: succinylcholine, tubocurarine;
- Any other corticosteroids.

How to take NETILDEX:

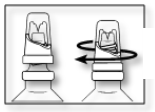
- NETILDEX is for topical use on the eye only.
- Although you may feel better early in treatment, NETILDEX should be used exactly as directed.
- Misuse or overuse of NETILDEX could lead to the growth of bacteria that will not be killed by NETILDEX (resistance). This means that NETILDEX may not work for you in the future.
- Do not share your medicine.

NETILDEX ophthalmic solution with preservative

Make sure the bottle is intact.

1. Wash your hands and sit comfortably.
2. Screw the cap down tightly in order to pierce the tip of the bottle. Unscrew the cap. **(Picture 1)**
3. Tilt your head back.
4. Use your finger to gently pull down the lower eyelid of your affected eye.
5. Invert the bottle and place the tip of the bottle close to, but not touching your eye. Do not touch your eye or eyelid with the dropper tip.
6. Squeeze the bottle gently in order to administrate only one drop, then release the lower eyelid. **(Picture 2)**
7. Repeat in the other eye if your doctor has told you to do so.
8. Put the cap back on the bottle. **(Picture 3)**

Picture 1



Picture 2

Picture 3

After first opening, do not use NETILDEX ophthalmic solution with preservative for more than 28 days.

If you incorrectly use the ophthalmic solution, it can become contaminated by bacteria which may lead to eye infections. Serious ocular damage and subsequent loss of vision may result from using contaminated ophthalmic solution.

Usual dose:

The usual dose is one drop in the affected eye(s) four times a day for 7 days, or as prescribed. Do not change the dose of the eye drops without consulting your doctor.

Overdose:

If you apply too much NETILDEX, rinse it out with warm water. Do not apply more NETILDEX until it is time for your next regular dose.

If you think you have used too much NETILDEX, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take NETILDEX, take it as soon as you remember. However, if it is close to your next regular dose, skip your missed dose and follow your regular schedule. Do not use a double dose to make up the missed dose.

What are possible side effects from using NETILDEX?

These are not all the possible side effects that you may feel when taking NETILDEX. If you experience any side effects not listed here, contact your healthcare professional.

Possible side effects include:
- Eyelid redness or swelling;
- Increased tearing;
- Dry eye;
- Eye irritation, pain, itching, inflammation, discomfort or redness;
- Blurred vision;
- Dizziness;
- Headache.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Allergic reaction: swelling of the face, lips or tongue; difficulty breathing; hives; skin redness, itching or blisters			✓
Inflammation of the eye (following cataract surgery): redness, pain, blurred vision	✓		
Infection			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Increased eye pressure and/or glaucoma, vision problems, or cataracts		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15 and 30°C. Keep out of reach and sight of children.

NETILDEX ophthalmic solution with preservative

After first opening, do not use this bottle for more than 28 days. When you are not using NETILDEX ophthalmic solution with preservative, keep the bottle in the outer carton, to protect it from light.

If you want more information about NETILDEX:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website, the distributor's website www.avirpharma.com, or by calling 1-888-430-0436.

This leaflet was prepared by:
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What are the ingredients in NETILDEX?

Preservative-free ophthalmic solution:

Medicinal ingredients: 0.3% w/v netilmicin (as netilmicin sulfate) and 0.1% w/v dexamethasone (as dexamethasone sodium phosphate).
Non-medicinal ingredients: disodium phosphate dodecahydrate, sodium citrate, monobasic sodium phosphate and purified water.

NETILDEX comes in the following dosage forms:

NETILDEX ophthalmic solution with preservative:

One bottle containing 5 ml of NETILDEX ophthalmic solution packed in a carton.

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- Have a fungal or parasitic infection of the eye.

- Have a mycobacterial infection of the eye, including tuberculosis.
- Have an active untreated eye infection.
- Recently had a simple removal of an object from the eye.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NETILDEX. Talk about any health conditions or problems you may have, including if you:

- Were advised by your healthcare provider that the pressure in your eye is too high (glaucoma).
- Have used other corticosteroids before in the past.
- Develop an allergic reaction. Signs may include skin redness, itching and rash. You should stop taking NETILDEX.
- Are taking another aminoglycoside antibiotic.
- Have diabetes. You may be at a higher risk of developing increased pressure in the eyes, vision problems or cataracts.
- Have a disease-causing thinning of your cornea (the front part of the eye) or sclera (white part of the eye). Small tears (*perforations*) have occurred.
- Have had damage to your cornea (the front part of the eye).
- Have recently had surgery on your eye. NETILDEX may cause blisters on your eye or delayed healing.
- Wear contact lenses. Contact lens wear is not recommended during treatment of eye inflammation or eye infection.
- Are pregnant, may be pregnant or planning to become pregnant.
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- Vision problems.
- Cataracts.
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- Any other antibiotics, in particular: aminoglycosides, penicillin, cephalosporin, polymyxin B, colistin, viomycin, streptomycin, vancomycin and cephaloridine;
- Cisplatin, an anti-cancer drug;
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- Anticholinergic medicines (medicines that stop glands secreting), such as atropine;
- Ritonavir (medicines used to treat HIV);
- Other medicines containing phosphates. Your doctor will check the cornea at regular intervals;
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- Botulinum toxin Type A, used to treat spasms, severe underarm sweat;
- Muscle relaxants, in particular: succinylcholine, tubocurarine;
- Any other corticosteroids.

How to take NETILDEX:

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- Although you may feel better early in treatment, NETILDEX should be used exactly as directed.
- Misuse or overuse of NETILDEX could lead to the growth of bacteria that will not be killed by NETILDEX (resistance). This means that NETILDEX may not work for you in the future.
- Do not share your medicine.

NETILDEX preservative-free ophthalmic solution

Make sure the preservative-free container is intact.

1. Wash your hands and sit or stand comfortably.
2. Separate the preservative-free container from the strip. **(Picture 1)**
3. Open by twisting the upper part without pulling. **(Picture 2)**
4. Tilt your head back.
5. Use your finger to gently pull down the lower eyelid of your affected eye.
6. Invert the preservative-free container and place the tip of the container close to, but not touching your eye. Do not touch your eye or eyelid with the container tip. **(Picture 3)**
7. Squeeze the preservative-free container in order to administrate only one drop, then release the lower eyelid.
8. Repeat in the other eye if your doctor has told you to do so.
9. Discard the preservative-free container after use.

Picture 1

Picture 2

Picture 3

NETILDEX preservative-free ophthalmic solution must be used immediately after opening. After administration, the preservative-free container and any unused content should be discarded.

If you incorrectly use the ophthalmic solution, it can become contaminated by bacteria which may lead to eye infections. Serious ocular damage and subsequent loss of vision may result from using contaminated ophthalmic solution.

Usual dose:

The usual dose is one drop in the affected eye(s) four times a day for 7 days, or as prescribed. Do not change the dose of the eye drops without consulting your doctor.

Overdose:

If you apply too much NETILDEX, rinse it out with warm water. Do not apply more NETILDEX until it is time for your next regular dose.

If you think you have used too much NETILDEX, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take NETILDEX, take it as soon as you remember. However, if it is close to your next regular dose, skip your missed dose and follow your regular schedule. Do not use a double dose to make up the missed dose.

What are possible side effects from using NETILDEX?

These are not all the possible side effects that you may feel when taking NETILDEX. If you experience any side effects not listed here, contact your healthcare professional.

Possible side effects include:

- Eyelid redness or swelling;
- Increased tearing;
- Dry eye;
- Eye irritation, pain, itching, inflammation, discomfort or redness;
- Blurred vision;
- Dizziness;
- Headache.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Allergic reaction: swelling of the face, lips or tongue; difficulty breathing; hives; skin redness, itching or blisters			✓
Inflammation of the eye (following cataract surgery): redness, pain, blurred vision	✓		
Infection			✓
Increased eye pressure and/or glaucoma, vision problems, or cataracts		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15 and 30°C. Keep out of reach and sight of children.

NETILDEX preservative-free ophthalmic solution

The product does not contain preservatives. NETILDEX preservative-free ophthalmic solution must be used immediately after opening. After administration, the preservative-free container and any unused content should be discarded. Store the remaining unused (and unopened) single-dose containers in the original package, to protect it from light.

If you want more information about NETILDEX:

- Talk to your healthcare professional.
  Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website, the distributor's website www.avirpharma.com, or by calling 1-888-430-0436.

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