Product Name: Polydex-N Eye Drops
(Dexamethasone, Neomycin & Polymyxin B Sulphate Eye Drops,
0.1% w/v / 3500 IU / 6000 IU)

1. Name of The Medicinal Product

Polydex-N Eye Drops

2. Qualitative and Quantitative Composition

1 ml drops contains 1 mg dexamethasone, 6000 IU polymyxin B sulphate, 3500 IU neomycin sulphate (as base).

Excipient(s) with known effect:

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Eye drops

4. Clinical Particulars

4.1 Therapeutic indications

Polydex-N eye drops is indicated for the short-term treatment of steroid responsive conditions of the eye when prophylactic antibiotic treatment is also required, after excluding the presence of fungal and viral disease.

4.2 Posology and method of administration

Children and Adults (including the Elderly)

Apply one or two drops to each affected eye up to six times daily or, more frequently if required.

Hepatic and renal impairment

Polydex-N Eye Drops has not been studied in these subject populations. However, due to low systemic absorption of the active substances after topical administration of this product, dose adjustment is not necessary.

Method of administration

For ocular use only. Not for injection or ingestion.

Shake the bottle well before use.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

In order to prevent contamination of the dropper tip and the suspension, caution should be exercised to ensure that the dropper tip does not touch the eyelids, the surroundings of the eye, or any other surfaces.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

4.3 Contraindications

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

As with all antibacterial preparation prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If super infection occurs, appropriate therapy should be initiated.

Sensitivity to topically applied aminoglycosides may occur in some patients. Cross-sensitivity to other aminoglycosides may also occur. Severity of hypersensitivity reactions may vary from local effects to generalized reactions such as erythema, itching, uticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If signs of serious reactions or hypersensitivity occur, discontinue the use of this product.

Patients using ophthalmic preparations containing neomycin sulphate should be advised to consult a physician if ocular pain, redness, swelling, or irritation worsens or persists.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic neomycin or when applied topically to open wounds or damaged skin. Nephrotoxic and neurotoxic reactions have also occurred with systemic polymyxin B. Although these effects have not been reported following topical ocular use of this product, caution is advised when used concomitantly with systemic aminoglycoside or polymyxin B therapy.

Prolonged use of 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. This is especially important in paediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults.

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

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, treatment should be progressively discontinued.

In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.

Corticosteroids may reduce resistance to and aid in the establishment of no susceptible bacterial, fungal, parasitic or viral infections and mask the clinical signs of infection or may suppress hypersensitivity reactions to Polydex-N eye drops. Fungal infection should be suspected in patients with persistent corneal ulceration who have been or are receiving these drugs; corticosteroid therapy should be discontinued if fungal infection occurs.

To avoid the risk of enhancement of herpetic corneal disease, frequent slit lamp examination is essential.

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).

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Contact lens wear is discouraged during treatment of an ocular infection. Therefore patients should be advised not to wear contact lenses during treatment with Polydex-N eye drops.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

CYP3A4 inhibitors (including ritonavir and cobicistat): may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

Concomitant and/or sequential use of an aminoglycoside (neomycin) and other systemic, oral, or topical drugs that have neurotoxic, ototoxic, or nephrotoxic effects may result in additive toxicity and should be avoided, whenever possible.

If more than one ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

The possibility of a higher need for hypoglycaemic medicinal products must be taken into consideration when administering diabetic patients because the hypoglycaemic effect of these medicinal products may be reduced (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility

There are no available data on the use of this medicine affecting male or female 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

There are no or limited amount of data from the use of eye drops in pregnant women.

Aminoglycoside antibiotics, such as neomycin, do cross the placenta after intravenous dosing in pregnant women. Non-clinical and clinical systemic exposure to aminoglycosides has been shown to induce ototoxicity and nephrotoxicity. At the low dose administered via this topical product, neomycin is not

expected to cause ototoxicity or nephrotoxicity 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 (See Section 4.4).

Studies in animals with some active components of eye drops have shown reproductive toxicity (see section 5.3).

Polydex-N eye drops is not recommended during pregnancy.

Lactation

It is unknown whether topical ophthalmic dexamethasone, neomycin or polymyxin B are excreted in human milk. Because systemic corticosteroids and aminoglycosides may be distributed into milk, a risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue/abstain from breast-feeding or to discontinue therapy with Polydex-N eye drops taking into account the benefit of breast-feeding for the child and the benefit of the product to the woman.

4.7 Effects on ability to drive and use machines

Polydex-N eye drops has no or negligible influence on the ability to drive and use machines. As with any other eye drop, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If transient blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials with Polydex-N eye drops the most common adverse reactions were ocular discomfort, keratitis, and eye irritation, occurring in 0.7% to 0.9% of patients.

Tabulated summary of adverse reactions

The following adverse reactions are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness. The adverse reactions were obtained from clinical trials and post-marketing experience for MAXITROL eye drops and MAXITROL eye ointment.

System Organ Classification	**MedDRA Preferred Term (v.18.0)**
Immune system disorders	*Not known:* hypersensitivity (systemic or ocular)
Endocrine disorders	*Not known:* Cushing's syndrome, adrenal suppression (see section 4.4)
Nervous system disorders	*Not known:* headache
Eye disorders	*Uncommon:* keratitis, intraocular pressure increased, eye pruritus, ocular discomfort, , eye irritation, *Not known:* ulcerative keratitis, corneal thinning, vision blurred (see also section 4.4), photophobia, mydriasis, eyelid ptosis, eye

	pain, eye swelling, foreign body sensation in eyes, ocular hyperaemia, increased lacrimation
Skin and subcutaneous tissue disorders	*Not known:* Stevens-Johnson syndrome

Description of selected adverse event

Due to the steroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments (See Section Special warnings and precautions for use).

Topical ophthalmic steroid use may result in increased intraocular pressure with damage to the optic nerve, reduced visual acuity and visual field defects. Also it may lead to posterior subcapsular cataract formation (See Section Special warnings and precautions for use).

Sensitivity to topically administered aminoglycosides may occur in some patients (See Section Special warnings and precautions for use). Systemic side effects may occur with extensive use.

Corticosteroids may impair glucose tolerance, which can lead to new-onset or exacerbation of diabetes mellitus (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No case of overdose has been reported.

Signs and symptoms of an overdosage of Polydex-N eye drops may be similar to adverse reaction effects seen in some patients (punctuate keratitis, erythema, increased lacrimation, oedema and lid itching).

Due to the characteristics of this preparation, intended for topical use, no toxic effects are expected when administered to the eye neither at the recommended dose nor in the event of accidental ingestion of the contents of a bottle.

A topical ophthalmic overdose of Polydex-N eye drops may be flushed from the eye(s) with lukewarm water.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ophthalmologicals; anti-infectives.

ATC code: S01CA01.

Product Name: Polydex-N Eye Drops
(Dexamethasone, Neomycin & Polymyxin B Sulphate Eye Drops,
0.1% w/v / 3500 IU / 6000 IU)

Mechanism of Action

Polydex-N eye drops has a dual effect: suppression of inflammation symptoms by the corticosteroidal component dexamethasone, and an anti-infective effect due to the presence of two antibiotics, polymyxin B and neomycin.

Dexamethasone is a synthetic glucorticoid with potent anti-inflammatory activity. Polymyxin B is a cyclic lipopeptide that penetrates the cell wall of gram-negative bacilli to destabilize the cytoplasmic membrane. It is generally less active against gram-positive bacteria. Neomycin is an aminoglycoside antibiotic that primarily exerts its effect on bacterial cells by inhibiting polypeptide assembly and synthesis on the ribosome.

Mechanism of Resistance

Resistance of bacteria to polymyxin B is of chromosomal origin and is uncommon. A modification of the phospholipids of the cytoplasmic membrane appears to play a role.

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

Breakpoints

Each gram of Polydex-N eye drops contains 6000 IU polymyxin B sulphate and 3500 IU neomycin sulphate. The breakpoints and the *in vitro* spectrum as mentioned below are based on the dual activity of either polymyxin B or neomycin. The breakpoints listed here are based upon acquired resistance for specific species found in ocular infections and the ratio in International Units of polymyxin B to neomycin in Polydex-N eye drops:

Resistance breakpoints: >5:2.5 to >40:20 depending upon the bacterial species.

Susceptibility

The information listed below provides guidance on the approximate probabilities on the susceptibility of microorganisms to polymyxin B or neomycin in Polydex-N. The presentation below lists bacterial species recovered from external ocular infections of the eye.

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 the combination of polymyxin B or neomycin as in Polydex-N eye drops in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive microorganisms
Bacillus cereus
Bacillus megaterium
Bacillus pumilus
Bacillus simplex
Corynebacterium accolens
Corynebacterium bovis
Corynebacterium macginleyi
Corynebacterium propinquum
Corynebacterium pseudodiphtheriticum
Staphylococcus aureus (methicillin susceptible - MSSA)

Staphylococcus capitis *Staphylococcus epidermidis* (methicillin susceptible - MSSE) *Staphylococcus pasteuri* *Staphylococcus warneri* *Streptococcus mutans* **Aerobic Gram-negative microorganisms** *Haemophilus influenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Moraxella lacunata* *Pseudomonas aeruginosa* *Serratia species*
SPECIES FOR WHICH ACQUIRED RESISTANCE MIGHT BE A PROBLEM *Staphylococcus epidermidis* (methicillin resistant - MRSE) *Staphylococcus hominis* *Staphylococcus lugdunensis*
INHERENTLY RESISTANT ORGANISMS **Aerobic Gram-positive microorganisms** *Enterococci faecalis* *Staphylococcus aureus* (methicillin resistant - MRSA) *Streptococcus mitis* *Streptococcus pneumoniae* **Anaerobic Bacteria** *Propionibacterium acnes*

Dexamethasone is a moderately powerful corticosteroid having good penetration in ocular tissue. Corticosteroids have an anti-inflammatory as well as a vasoconstrictive effect. They suppress the inflammatory response and symptoms in various disorders without basically curing these disorders.

5.2 Pharmacokinetic properties

Dexamethasone, like other corticosteroids, is absorbed rapidly after oral administration and has a biological half-life of about 190 minutes. Sufficient absorption may occur after topical application to the skin and eye to produce systemic effects. Intraocular penetration of dexamethasone occurs in significant amounts and contributes to the effectiveness of dexamethasone in anterior segment inflammatory disease.

Polymyxin B sulphate is not absorbed from the gastrointestinal tract or through intact skin, although the intact corneal epithelium prevents penetration into the corneal stroma, therapeutic concentrations do enter the stroma after epithelial damage. Good stromal penetration occurs after epithelial abrasion following topical instillation, subconjunctival injection, or corneal bath. No significant polymyxin B penetration into the vitreous is demonstrable after parenteral or local administration of the drug.

Neomycin is poorly absorbed from the gastrointestinal tract and after topical administration an insufficient amount is absorbed to produce systemic effects. Absorption has been reported to occur from wounds and inflamed skin. After absorption neomycin is rapidly excreted by the kidneys in active form.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of excipients

- Hydroxypropyl Methylcellulose (4000 CPs)
- Benzalkonium Chloride Solution
- Sodium Chloride
- Hydrochloric Acid
- Sodium Hydroxide
- Water for Injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

LDPE droper bottle

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorisation Holder

Name	:	Aristopharma Ltd.
Principal office	:	7 Purana Paltan Line, Dhaka-1000, Bangladesh
Site of manufacturer	:	Plot # 14- 22, Road # 11 & 12, Shampur-Kadamtali I/A, Dhaka-1204, Bangladesh
Telephone number	:	+880-2-9351691-93
Fax number	:	+880-2-8317005
e-mail	:	parvez@aristopharmabd.com

8. Marketing Authorisation Number

Polydex-N Eye Drops: 143–166–052

9. Date of First Authorisation

Date of first authorisation : 11–06–2002

10. Date of Revision of the Text

To be given after approval of the product