PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BETNESOL-N EYE, EAR AND NOSE DROPS 100 mg, 350 mg / 100 ml solution

2. QUALITATIVE AND QUANTITATIVE

Each 100 ml contains:

Betamethasone sodium phosphate 100 mg

Neomycin sulphate equivalent to 350 mg neomycin base

Benzalkonium chloride 0,01 % *m/v* as preservative

Excipients with known effect:

Disodium hydrogen phosphate heptahydrate 0,377 % *m/v*

Sodium acid phosphate 0.03 % *m/v*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution

BETNESOL-N EYE, EAR AND NOSE DROPS is a clear, colourless to pale yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eye conditions: Non-infected inflammatory conditions such as non-specific keratitis, conjunctival allergies and acute or chronic uveitis.

Ear conditions: inflammatory conditions of the ear such as otitis externa where bacterial infection is present or probable (see section 4.3)

Nasal conditions: Hayfever, vasomotor and non-seasonal allergic rhinitis. Steroid responsive inflammatory conditions where infection is present or suspected.

4.2 Posology and method of administration

Posology

EYE: One or two drops to be instilled into the eye every one or two hours until control is achieved, then the frequency may be reduced.

EAR: Two to three drops to be instilled into the ear every two or three hours until control is achieved, then the frequency may be reduced.

NOSE: Two or three drops to be instilled into each nostril two or three times daily.

Because of the possibility of inducing corneal abscess, fungal keratopathy or glaucoma, the patient should be referred to an ophthalmologist if the eye has not responded within 48 hours (see section 4.4 and 4.8).

Paediatric population

BETNESOL-N EYE, EAR AND NOSE DROPS is suitable for use in children at the same dose as adults, but the dose should be reduced in infants.
BETNESOL-N EYE, EAR AND NOSE DROPS is not recommended for use in neonates (see section 4.3 and 4.4).

Due to the growth retardation that has been reported in children receiving nasal corticosteroids such as BETNESOL-N EYE, EAR AND NOSE DROPS, the lowest dose at which effective control of symptoms is maintained should be used. Additionally, consideration should also be given to referring the patient to a paediatric specialist. (see section 4.4 and 4.8).
In infants, long-term continuous topical therapy should be avoided where possible, as adrenal suppression can occur even without occlusion. The least potent corticosteroid which will control the disease should be selected (see section 4.4 and 4.8)

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Viral, fungal, tuberculous and purulent infections.
- Possibility of herpetic keratitis.
- Glaucoma.

- Due to the risk of ototoxicity, preparations containing neomycin should not be used until an intact tympanic membrane has been visualised.
- BETNESOL-N EYE, EAR AND NOSE DROPS contain benzalkonium chloride as a preservative and therefore should not be used to treat patients who wear soft lenses (see section 4.4).
- A possibility of increased absorption exists in very young children, thus Betnesol-N EYE, EAR AND NOSE DROPS is not recommended for use in neonates (see 4.2 and 4.4)
- BETNESOL-N EYE, EAR AND NOSE DROPS is not recommended in pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Do not administer to “red eyes” until a definitive diagnosis is made as inappropriate use could lead to blindness.

Treatment with corticosteroid preparations should not be repeated or prolonged without regular review to exclude raised intraocular pressure, cataract formation or unsuspected infections (see section 4.2 and 4.8).

Treatment with corticosteroid/antibiotic combinations should not be continued for more than 7 days in the absence of any clinical improvement, since prolonged use may lead to occult extension of infection due to the masking effect of the steroid (see 4.2 and 4.8).

Prolonged use may also lead to skin sensitisation.

The unnecessary topical use of neomycin-containing products should be avoided in order to minimise occurrence of neomycin resistant organisms.

Acute sensitisation to neomycin has been reported.

Eye preparations containing corticosteroids can cause a serious rise in intra-ocular pressure in a small percentage of the population. A milder rise in ocular tension may be experienced by a larger proportion of subjects if treatment is continued for no longer than a few weeks (see section 4.8).

Because of the possibility of inducing corneal abscess, fungal keratopathy or glaucoma, the patient should be referred to an ophthalmologist if the eye has not responded within 48 hours (see section 4.2 and 4.8).

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 (see section 4.2 and 4.8).

In diseases causing thinning of the cornea, perforation has occurred with use of ophthalmic corticosteroids (see section 4.5, and 4.8).
Cataract is reported to have occurred after unduly prolonged treatment of eye conditions with ophthalmic corticosteroids.

Aminoglycoside antibiotics, such as the neomycin in BETNESOL-N EYE, EAR AND NOSE DROPS may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment (see section 4.8). Although this effect has not been reported following topical ocular use, the possibility should be considered when high dose topical treatment is given to infants or small children.
There have been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A>G
mutation, including cases where the patient's aminoglycoside serum levels were within the recommended range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation (see section 4.5 and 4.8). While no cases were identified with neomycin, based on a shared mechanism of action there is the potential for a similar effect with neomycin.

These mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

Nasal administration of corticosteroids is not advised if an untreated nasal infection is present or if the patient has pulmonary tuberculosis or following nasal surgery (until healing has occurred).

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations (See section 4.8).

Warnings related to the preservative and phosphates in the formulation

- Due to the benzalkonium chloride preservative in BETNESOL-N EYE, EAR AND NOSE DROPS, it should not be used to treat patients who wear soft lenses (see section 4.3).
- As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required (see section 4.8)
- Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease (see section 4.5).
- Benzalkonium chloride may also cause eye irritation, especially in patients with dry eyes or disorders of the cornea**.** It may also cause irritation or swelling inside the nose, especially if used for a prolonged periods (see section 4.8).
- This medicine contains 4,07 mg phosphates in each millilitre of solution which is equivalent to 4,07 mg/ml. In patients suffering from severe damage to the cornea, phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment (See section 4.8).

Paediatric population

In infants, long-term continuous topical therapy should be avoided where possible, as adrenal suppression can occur even without occlusion. The least potent corticosteroid which will control the disease should be selected (see section 4.2 and 4.8)

In neonates and infants, absorption by immature skin may be enhanced and renal function may be immature (see section 4.3). For this reason, BETNESOL-N EYE, EAR AND NOSE DROPS is contraindicated in neonates (see section 4.2)

Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroids, if possible, to the lowest dose at which effective control of symptoms is maintained.

In addition, consideration should also be given to referring the patient to a paediatric specialist (see section 4.2 and 4.8)

4.5 Interaction with other medicines and other forms of interaction

Co-treatment with CYP3A inhibitors, including cobicistat containing products, is expected to increase the risk of systemic side-effects. 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 side-effects.

BETNESOL-N EYE, EAR AND NOSE DROPS contains benzalkonium chloride as a preservative and therefore, should not be used to treat patients who wear soft contact lenses (see section 4.3 and 4.4).

Special populations

In diseases causing thinning of the cornea, perforation has occurred with use of ophthalmic corticosteroids (see section 4.4 and 4.8).

In those diseases causing thinning of the cornea or sclera, use of BETNESOL-N EYE, EAR AND NOSE DROPS may result in thinning of the globe leading to perforation (see section 4.4).

There have been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A>G mutation, including cases where the patient's aminoglycoside serum levels were within the recommended range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation (see section 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

Corticosteroids included in BETNESOL-N EYE, EAR AND NOSE DROPS have been shown to be teratogenic in animals following dermal application. As these medicines are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore, BETNESOL-N EYE, EAR AND NOSE DROPS should not be used during pregnancy (see section 4.3).

There is little information to demonstrate the possible effect of topically applied neomycin in pregnancy and lactation. However neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal ototoxicity. For this reason, BETNESOL-N EYE, EAR AND NOSE DROPS is not recommended in pregnancy and lactation.

Breastfeeding

BETNESOL-N EYE, EAR AND NOSE DROPS should not be used while breastfeeding (see section 4.3).

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

May cause transient blurring of vision on instillation. Patients should be warned not to drive or operate hazardous machinery unless vision is clear.

BETNESOL-N EYE, EAR AND NOSE DROPS has a moderate influence on the ability to drive and use machines

4.8 Undesirable effects

a) Summary of the safety profile

Treatment with corticosteroid preparations should not be prolonged without regular review to exclude raised intraocular pressure, cataract formation, unsuspected infections, occult extension of infection due to the masking effect of the steroid, skin sensitization, the emergence of resistant organisms and irritation or swelling inside the nose (see section 4.2 and 4.4).

The irreversible, partial or total deafness that is a possible side effect due to the neomycin (an aminoglycoside antibiotic) in BETNESOL-N EYE, EAR AND NOSE DROPS effect is dose related and is enhanced by renal or hepatic impairment (see section 4.4).

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations (see section 4.4)

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and Infestations			Unsuspected infections, occult extension of infection due to the masking effect of the steroid (see section 4.4)
Immune system disorders			Acute sensitization to neomycin (see section 4.4).
Endocrine disorders			Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents.
Psychiatric disorders			Psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children)
Eye disorders	Mild rise in ocular tension (see section 4.8 c).	Serious rise in intra-ocular pressure (see section 4.8 c).	Blindness, raised intraocular pressure, cataracts, corneal abscess, fungal keratopathy, glaucoma, blurred vision, visual disturbances, central serous chorioretinopathy (CSCR), corneal perforation, thinning of the globe leading to perforation adverse effects on corneal permeability, disruption of the corneal epithelium, eye irritation, cloudy patches on the cornea due to calcium build-up, (see section 4.4). Corneal ulceration, mydriasis, ptosis, epithelial punctate keratitis.
Ear and labyrinth disorders		Ototoxicity (see section 4.4).	Irreversible, partial or total deafness (see section 4.4).
Respiratory, thoracic and			Irritation or swelling inside the nose (see section 4.4), bronchial asthma.

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Mediastinal disorders			
Gastrointestinal disorders			Nausea
Skin and subcutaneous tissue disorders			Skin sensitization (see section 4.4), urticaria.
General disorders and administrative site conditions	Nasal dryness and irritation		Sneezing, headache, light-headedness, epistaxis, rebound congestion, perforation of the nasal septum, ulceration of the nasal septum, smell and taste disturbances. Hypersensitivity that results in irritation, burning, stinging, itching and dermatitis.

c) Description of selected adverse reactions

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 (see section 4.4).

Eye preparations such as BETNESOL-N EYE, EAR AND NOSE DROPS can cause a serious rise in intra-ocular pressure in a small percentage of the population. A milder rise in ocular tension may be experienced by a larger proportion of subjects if treatment is continued for no longer than a few weeks (see section 4.4).

d) Paediatric population

In infants, long-term continuous topical therapy should be avoided where possible due to the adrenal suppression that can occur.

If growth is slowed, therapy should be reviewed with the aim of reducing the dose (see section 4.2 and 4.4).

e) Other special population(s)

The benzalkonium chloride included as a preservative in BETNESOL-N EYE, EAR AND NOSE DROPS may also cause eye irritation, especially in patients with dry eyes or disorders of the cornea.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas (see section 4.4).

Patients with a maternal history of deafness and/or mitochondrial mutation have an increased risk of ototoxicity (see section 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

Reporting can also be done directly to Adcock Ingram Limited at:

Adcock Ingram Limited:

E-mail: Adcock.aereports@adcock.com

Tel: 011 635 0134

4.9 Overdose

The quantity of betamethasone sodium phosphate present is such that systemic absorption is unlikely to occur to any significant extent. In these circumstances, overdosage is unlikely, although appropriate care should be taken as noted under Undesirable effects and Special warnings and precautions for use (see sections 4.8 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

BETNESOL-N EYE, EAR AND NOSE DROPS contain the water-soluble corticosteroid betamethasone sodium phosphate, and have the advantage of containing no steroid particles to cause irritation. This is of particular value in ophthalmic work. The presence of neomycin may prevent the development of bacterial infection.

5.1 Pharmacodynamic properties

Category and Class: A. 15.3 Combined antibiotic and corticosteroid ophthalmic preparation.
Pharmacotherapeutic group: Corticosteroids and anti-infectives in combination – betamethasone and anti-infectives
ATC code: S03CA06

Pharmacokinetic properties

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, disodium edetate, disodium hydrogen phosphate heptahydrate, phosphoric acid (for pH-adjustment) polyethylene glycol 300, sodium acid phosphate, sodium formate, sodium hydroxide (for pH-adjustment), sodium sulphate anhydrous, water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months if kept in the original packaging and stored at or below 25 °C.
The shelf life after opening is 28 days.

6.4 Special precautions for storage

Store at or below 25 °C
Protect from light.
Avoid freezing.
Eye drops should be discarded within 28 days of first opening the container.

6.5 Nature and contents of container

5 ml or 10 ml solution is packed into an opaque low density polyethylene bottle with an opaque low density polyethylene drop applicator, and sealed with a white polypropylene tamper evident cap. The sealed bottles are packed into unit cartons together with a leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand,1685
Customer Care: 0860 ADCOCK/ 232625

8. REGISTRATION NUMBER

H1258 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Old medicine

10. DATE OF REVISION OF THE TEXT

21 October 2022

Namibia		
NS2	BETNESOL-N EYE, EAR AND NOSE DROPS	14/15.3/0609