1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. **NAME OF THE MEDICINAL PRODUCT**
   BETNACIN – EEN EYE/EAR/NASAL DROPS (Betamethasone & Neomycin Eye/Ear/Nasal Drops)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative Declaration:

Betamethasone & Neomycin Eye/Ear/Nasal Drops

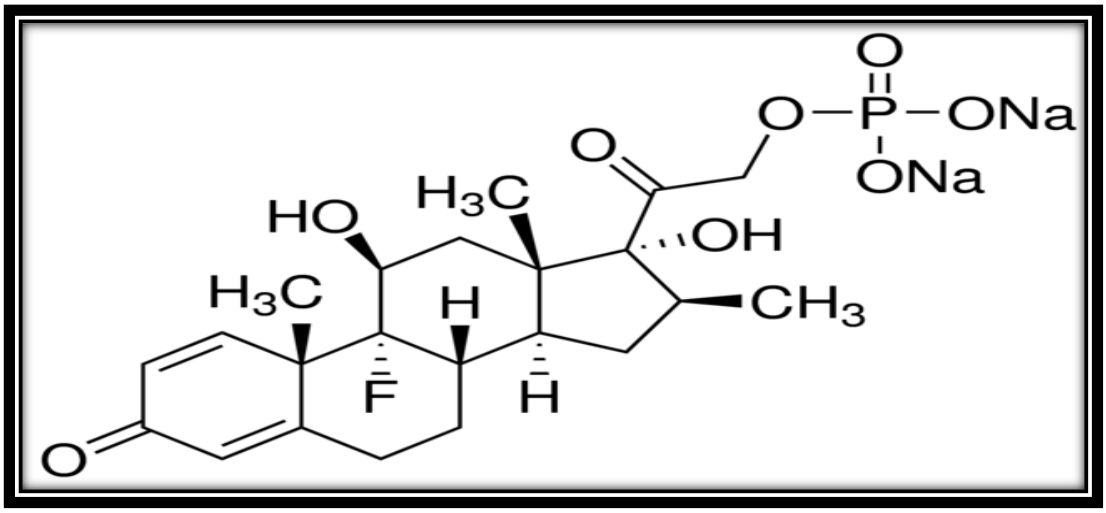
- **Betamethasone Sodium Phosphate:**

Chemical Name:
Disodium (11β,16β)-9-fluoro-11,17-dihydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-yl phosphate

Molecular weight: 516.41 g/mol

Molecular formula: $C_{22}H_{28}FNa_2O_8P$

Structural Formula:-



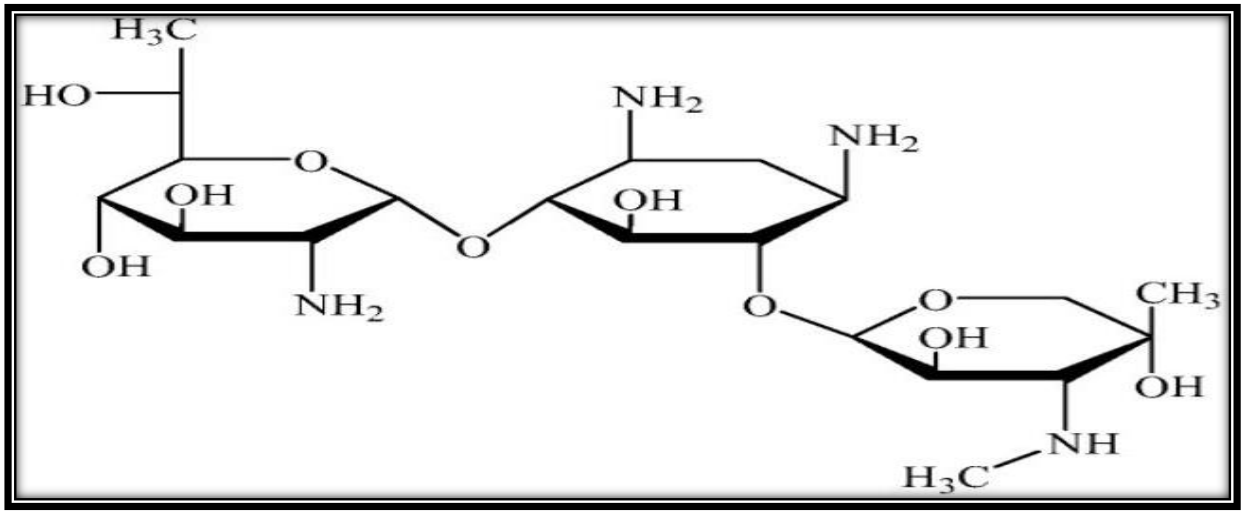
- **Neomycin Sulfate:**

Chemical Name:
(2*RS*,3*S*,4*S*,5*R*)-5-amino-2-(aminomethyl)-6-((2*R*,3*S*,4*R*,5*S*)-5-((1*R*,2*R*,5*R*,6*R*)-3,5-diamino-2-((2*R*,3*S*,4*R*,5*S*)-3-amino-6-(aminomethyl)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yloxy)-6-hydroxycyclohexyloxy)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yloxy)tetrahydro-2*H*-pyran-3,4-diol

Molecular weight: 616.644 g/mol

Molecular formula: $C_{23}H_{46}N_6O_{13}$

Structural Formula:-



Pharmaceutical Form Visual description of the appearance of product:
Clear colourless to yellowish solution, free from any type of visible particles.

Quantitative Declaration:

Composition: w/v

Betamethasone Sodium Phosphate	USP	0.1% w/v
Neomycin Sulfate	USP	0.5% w/v
Methyl Paraben (As Preservative)	NF	0.02% w/v
Propyl Paraben (As Preservative)	NF	0.005% w/v
Sterile aqueous base		Q.S

3. PHARMACEUTICAL FORM

Eye/Ear/Nasal Drops

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Eye

Short-term treatment of steroid responsive inflammatory conditions of the eye when prophylactic antibiotic treatment is also required, after excluding the presence of viral and fungal disease.

Ear

Otitis externa or other steroid responsive conditions where prophylactic antibiotic treatment is also required.

Nose

Steroid responsive inflammatory conditions where prophylactic antibiotic treatment is also required.

4.2 Posology and method of administration
DOSAGE AND ADMINISTRATION

The frequency of dosing depends on the clinical response. If there is no clinical response within 7 days of treatment, the drops should be discontinued.

Treatment should be the lowest effective dose for the shortest possible time. After more prolonged treatment (over 6 to 8 weeks), the drops should be withdrawn slowly to avoid relapse.

Eyes

1 or 2 drops applied to each affected eye up to six times daily depending on clinical response.

Ears

2 or 3 drops instilled into the ear three or four times daily.

Nose

2 or 3 drops instilled into each nostril two or three times daily

4.3 Contraindications

Viral, fungal, tuberculous or purulent conditions of the eye. Fungal infections of the nose or ear. Use is contra-indicated if glaucoma is present or herpetic keratitis (e.g. dendritic ulcer) is considered a possibility. Use of topical steroids in the latter condition can lead to an extension of the ulcer and marked visual deterioration.

Otitis externa should not be treated when the eardrum is perforated because of the risk of ototoxicity.

Corticosteroids should not be used in patients with a perforated tympanic membrane.

Hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

Topical corticosteroids should never be given for an undiagnosed red eye as inappropriate use is potentially blinding.

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. Prolonged use may also lead to skin sensitisation and the emergence of resistant organisms.

Ophthalmological treatment with corticosteroid preparations should not be repeated or prolonged without regular review to exclude raised intraocular pressure, cataract formation or unsuspected infections.

Aminoglycoside antibiotics 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. Although this effect has not been reported following topical ocular use, the possibility should be considered when high dose topical treatment is given to small children or infants.

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. 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. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

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.

4.5 Interaction with other medicinal products 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.

4.6 Fertility, pregnancy and lactation

Safety for use in pregnancy and lactation has not been established. There is inadequate evidence of safety in human pregnancy. Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate and intrauterine growth retardation. There may therefore be a very small risk of such effects in the human foetus.

There is a risk of foetal ototoxicity if aminoglycoside antibiotic preparations are administered during pregnancy.

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.

4.8 Undesirable effects

Hypersensitivity reactions, usually of the delayed type, may occur leading to irritation, burning, stinging, itching and dermatitis.

Topical corticosteroid use may result in corneal ulceration, increased intraocular pressure leading to optic nerve damage, reduced visual acuity and visual field defects.

Intensive or prolonged use of topical corticosteroids may lead to formation of posterior subcapsular cataracts.

In those diseases causing thinning of the cornea or sclera, corticosteroid therapy may result in thinning of the globe leading to perforation.

Mydriasis, ptosis, epithelial punctate keratitis and glaucoma have also been reported following ophthalmic use of corticosteroids.

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.

Following nasal administration, the most common effects are nasal irritation and dryness, although sneezing, headache, lightheadedness, urticaria, nausea, epistaxis, rebound congestion, bronchial asthma, perforation of the nasal septum, ulceration of the nasal septum, anosmia, parosmia and disturbance to sense of taste have also been reported.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. 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 corticosteroid, 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.

Vision, blurred (see also 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 Yellow Card Scheme on the MHRA website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Long-term intensive topical use may lead to systemic effects.

Oral ingestion of the contents of one bottle (up to 10ml) is unlikely to lead to any serious adverse effects.

Treatment with higher than recommended doses may result in clinically significant adrenal suppression. If there is evidence of higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacodynamic properties:

Betamethasone Sodium Phosphate:

Pharmacotherapeutic group: Glucocorticosteroid

ATC code: S01BA06

Pharmacodynamic properties:

Betamethasone and its derivatives, betamethasone sodium phosphate and betamethasone acetate, are synthetic glucocorticoids. Used for its antiinflammatory or immunosuppressive properties, betamethasone is combined with a mineralocorticoid to manage adrenal insufficiency and is used in the form of betamethasone benzoate, betamethasone dipropionate, or betamethasone valerate for the treatment of inflammation due to corticosteroid-responsive dermatoses. Betamethasone and clotrimazole are used together to treat cutaneous tinea infections.

Mechanism of action:

Betamethasone is a glucocorticoid receptor agonist. This leads to changes in genetic expression once this complex binds to the GRE. The antiinflammatory actions of corticosteroids are thought to involve lipocortins, phospholipase A2 inhibitory proteins which, through inhibition arachidonic acid, control the biosynthesis of prostaglandins and leukotrienes. The immune system is suppressed by corticosteroids due to a decrease in the function of the lymphatic system, a reduction in immunoglobulin and complement concentrations, the precipitation of lymphocytopenia, and interference with antigen-antibody binding. Betamethasone binds to plasma transcortin, and it becomes active when it is not bound to transcortin.

Application:

Betamethasone is a corticosteroid that is available as pill, by injection, and as a cream.

It is used as a topical cream to relieve skin irritation, such as itching and flaking from eczema. It is used as a treatment for local psoriasis, as betamethasone dipropionate and salicylic acid, or as the combination calcipotriol/betamethasone dipropionate. Betamethasone sodium phosphate is used orally and via injection with the same indications as other steroids. Many betamethasone-based pharmaceuticals include the steroid as the valerate ester.

In a randomized controlled trial betamethasone was shown to reduce some of the ataxia symptoms associated with ataxia telangiectasia (A-T) by 28-31%.

Betamethasone is also used to stimulate fetal lung maturation (to prevent IRDS), and to decrease the incidence and mortality from intracranial hemorrhage in premature infants.

A cream with 0.05% betamethasone appears effective in treating phimosis in boys, and often averts the need for circumcision. It has replaced circumcision as the preferred treatment method for some physicians in the British National Health Service.

Neomycin Sulphate

Pharmacotherapeutic group: Antibiotic

ATC code: S01AA03

Pharmacodynamic properties:

Neomycin is an aminoglycoside antibiotic. Aminoglycosides work by binding to the bacterial 30S ribosomal subunit, causing misreading of t-RNA, leaving the bacterium unable to synthesize proteins vital to its growth. Aminoglycosides are useful primarily in infections involving aerobic, Gram-negative bacteria, such as Pseudomonas, Acinetobacter, and Enterobacter. In addition, some mycobacteria, including the bacteria that cause tuberculosis, are susceptible to aminoglycosides. Infections caused by Gram-positive bacteria can also be treated with aminoglycosides, but other types of antibiotics are more potent and less damaging to the host. In the past the aminoglycosides have been used in conjunction with penicillin-related antibiotics in streptococcal infections for their synergistic effects, particularly in endocarditis. Aminoglycosides are mostly ineffective against anaerobic bacteria, fungi and viruses.

Mechanism of action:

Aminoglycosides like neomycin "irreversibly" bind to specific 30S-subunit proteins and 16S rRNA. Specifically neomycin binds to four nucleotides of 16S rRNA and a single amino acid of protein S12. This interferes with decoding site in the vicinity of nucleotide 1400 in 16S rRNA of 30S subunit. This region interacts with the wobble base in the anticodon of tRNA. This leads to interference with the initiation complex, misreading of mRNA so incorrect amino acids are inserted into the polypeptide leading to nonfunctional or toxic peptides and the breakup of polysomes into nonfunctional monosomes.

Application:

Neomycin is typically used as a topical preparation, such as Neosporin. It can also be given orally, where it is usually combined with other antibiotics. Neomycin is not absorbed from the gastrointestinal tract and has been used as a preventive measure for hepatic encephalopathy and hypercholesterolemia. By killing bacteria in the intestinal tract, it keeps ammonia levels low and prevents hepatic encephalopathy, especially prior to GI surgery. It has also been used to treat small intestinal bacterial overgrowth. It is not given via injection, as neomycin is extremely nephrotoxic (causes kidney damage), even when compared to other aminoglycosides. The exception is when neomycin is included, in very small quantities, as a preservative in some vaccines – typically 25 mg per dose.

5.2 Pharmacokinetics Properties

Not applicable as the drops are applied topically.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MATERIAL NAME	SPECS.
METHYL PARABEN (SODIUM SALT)	NF
PROPYL PARABEN (SODIUM SALT)	NF
SODIUM CHLORIDE	BP/USP NF
EDETATE DISODIUM	NF
SODIUM METABISULPHITE	NF
SODIUM DIHYDROGEN PHOSPHATE	BP
ANHYDROUS DISODIUM HYDROGEN PHOSPHATE	BP
POLYETHYLENE GLYCOL 400 (PEG-400)	NF
SODIUM HYDROXIDE PELLETS	NF
PURIFIED WATER	BP/IH

6.2 Shelf life

24 months

6.3 Special precautions for storage

Store below 30 degrees C.
Do not freeze.
Protect from light.
Keep out of the reach of children.

6.4 Nature and contents of container

The liquid is filled in a multi dose container, and contain Methyl Paraben, Propyl paraben, Sodium Chloride, Edetate Disodium, Sodium Metabisulphite, Sodium Dihydrogen Phosphate, Anhydrous Disodium Hydrogen Phosphate, Polyethylene Glycol 400, Sodium Hydroxide Pellets for pH Adjustment.

Solution is filled in 10 ml Opaque sterile plastic bottle (LDPE).

6.5 Special precaution for disposal of a used medicinal product or waste materials derived such medicinal product and other handling of the product

No special requirements

7.0 Name and complete address (es) of the Applicant & manufacturer(s) of the FPP

Applicant

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