For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

BETNOVATE - N

1. GENERIC NAME

Betamethasone Valerate and Neomycin Skin Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Neomycin Sulphate I.P. 0.5% w/w
Chlorocresol I.P. 0.1% w/w (as preservative) in a non-greasy base

3. DOSAGE FORM AND STRENGTH

Cream

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Neomycin Sulphate I.P. 0.5% w/w
Chlorocresol I.P. 0.1% w/w (as preservative) in a non-greasy base

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Betamethasone valerate is a potent topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses. Neomycin sulphate is an aminoglycoside broad spectrum antibiotic.

Topical preparations combining betamethasone valerate and neomycin sulphate are indicated for the treatment of the following conditions where secondary bacterial infection is present, suspected, or likely to occur:

- Atopic dermatitis
- Nummular dermatitis (discoid eczema)
- Prurigo nodularis
- Psoriasis (excluding widespread plaque psoriasis)
- Lichen simplex chronicus (neurodermatitis) and lichen planus
- Seborrhoeic dermatitis
- Irritant or allergic contact dermatitis
- Insect bite reactions
- Miliaria (prickly heat)
- Anal and genital intertrigo
- Otitis externa (se*e 4.3 Contraindications*).

4.2 Posology and Method of Administration

BETNOVATE-N cream is especially appropriate for moist or weeping surfaces.

Adults and adolescents

Apply thinly and gently rub in using enough to cover the entire affected area once or twice daily for up to seven days, then change to another corticosteroid preparation not containing neomycin sulphate if further treatment is required. Allow adequate time for absorption after each application before applying an emollient.

In the more resistant lesions, such as the thickened plaques of psoriasis on elbows and knees, the effect of *BETNOVATE-N* can be enhanced, if necessary, by occluding the treatment area with polythene film. Overnight occlusion only is usually adequate to bring about a satisfactory response in such lesions, thereafter improvement can usually be maintained by regular application without occlusion.

Treatment should not be continued for more than seven days without medical supervision. If the condition worsens or does not improve within seven days, treatment and diagnosis should be re-evaluated.

Children aged 2 years and over

BETNOVATE-N is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus *BETNOVATE-N* is contraindicated in neonates and infants (less than 2 years) (see *4.3 Contraindications*).

Children are more likely to develop local and systemic side effects of topical corticosteroids and, in general, require shorter courses and less potent agents than adults.

Care should be taken when using *BETNOVATE-N* to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

BETNOVATE-N is suitable for use in the elderly. Clinical studies have not identified difference in responses between the elderly and younger patients. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs. Therefore, the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

Renal Impairment

Dosage should be reduced in patients with reduced renal function *(*see *4.4 Special Warnings and Precautions for Use*).

4.3. Contraindications

BETNOVATE-N is contraindicated in children under 2 years of age.

Due to the known ototoxic and nephrotoxic potential of neomycin sulphate, the use of *BETNOVATE-N* in large quantities or on large areas for prolonged periods of time is contraindicated in circumstances where significant systemic absorption may occur (see *4.2 Posology and Method of Administration*).
The following conditions should not be treated with *BETNOVATE-N*:

- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Pruritus without inflammation
- Perianal and genital pruritus
- Primary cutaneous viral infections
- Primary infected skin lesions caused by infection with fungi, or bacteria
- Primary or secondary infections due to yeasts
- Secondary infections due to *Pseudomonas* or *Proteus* species
- Otitis externa when the ear drum is perforated, because of the risk of ototoxicity

4.4 Special Warnings and Precautions for Use

Hypersensitivity

BETNOVATE-N should be used with caution in patients with a history of local hypersensitivity to betamethasone, neomycin or to any of the excipients in the preparation. Local hypersensitivity reactions (see *4.8 Undesirable Effects*) may resemble symptoms of the condition under treatment.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. Although this is less likely to occur with topically applied *BETNOVATE-N*. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression

Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression can occur in some individuals as a result of increased systemic absorption of topical corticosteroids. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency (see *4.8 Undesirable Effects*).

Risk factors for increased corticosteroidal systemic effects are:

- Potency and formulation of topical corticosteroid
- Duration of exposure
- Application to a large surface area

- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (nappies may act as an occlusive dressing)
- Increasing hydration of the stratum corneum
- Use on thin skin areas such as the face
- Use on broken skin or other conditions where the skin barrier may be impaired.

Visual disturbances

Visual disturbance has been reported by patients using systemic and / or topical corticosteroids. If a patient has blurred vision or other visual disturbances, consider evaluation of possible causes which may include cataract, glaucoma or central serous chorioretinopathy.

Use in children

In comparison with adults, children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a greater surface area to body weight ratio compared with adults.

In children under 12 years of age, long term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.

Use in psoriasis

Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerance, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases (see *4.8 Undesirable Effects*). If used in psoriasis careful patient supervision is important.

Dilution

Products which contain antimicrobial agents should not be diluted.

Contact sensitisation

Extended or recurrent application of *BETNOVATE-N* may increase the risk of contact sensitisation.

Ototoxicity and nephrotoxicity

Following significant systemic absorption, aminoglycosides such as neomycin can cause irreversible ototoxicity. Neomycin also has nephrotoxic potential *(*see *4.3 Contraindications).*

Renal impairment

In renal impairment the plasma clearance of neomycin is reduced (see *4.2 Posology and Method of Administration).*

Application to the face

Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes.

Application to the eyelids

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as cataract and glaucoma might result from repeated exposure.

Infection

Extension of infection may occur due to the masking effect of the steroid. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate systemic antimicrobial therapy.

Infection risk with occlusion

Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings. When using occlusive dressings, the skin should be cleansed before a fresh dressing is applied.

Chronic leg ulcers

Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Flammability risk

BETNOVATE-N cream contain paraffin. Instruct patients not to smoke or go near naked flames due to the risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

4.5 Drug Interactions

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

Following significant systemic absorption, neomycin sulphate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents.

Possibility of cumulative toxicity should be considered when neomycin sulphate is applied topically in combination with systemic aminoglycoside therapy.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Fertility

There are no data in humans to evaluate the effect of *BETNOVATE-N* fertility.

Pregnancy

There are limited data from the use of *BETNOVATE-N* in pregnant women.

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see *6. Nonclinical properties*). The relevance of this finding to humans has not been established.

However, neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity (see *6. Nonclinical properties*). Thus, use of *BETNOVATE-N* is not recommended in pregnancy.

Lactation

The safe use of *BETNOVATE-N* during lactation has not been established.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Thus, use of *BETNOVATE-N* is not recommended in lactation.

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *BETNOVATE-N* on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of topical *BETNOVATE-N.*

4.8 Undesirable Effects

Clinical Trial and Post-marketing Data

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Infections and Infestations

Very rare	Opportunistic infection

Immune System Disorders

Very rare	Local hypersensitivity

Endocrine Disorders

Very rare	Hypothalamic-pituitary adrenal (HPA) axis suppression: (see also *Skin and Subcutaneous Tissue Disorders*) Cushingoid features (e.g. moon face, central obesity), delayed weight gain/growth retardation in children, osteoporosis,

	glaucoma, hyperglycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels

Skin and Subcutaneous Tissue Disorders

Common	Pruritus, local skin burning/pain of skin
Very rare	Allergic contact dermatitis/dermatitis, erythema, rash, urticaria, pustular psoriasis (see *4.4 Special Warnings and Precautions for Use)*, skin thinning* / skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, alopecia*, trichorrhexis*

General Disorders and Administration Site Conditions

Very rare	Application site irritation/pain

**Skin features of hypothalamic-pituitary-adrenal (HPA) axis suppression.*

4.9 Overdose

Symptoms and signs

Topically applied *BETNOVATE-N* may be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the features of hypercortisolism may occur (see *4.8 Undesirable Effects*).

Treatment

In the event of chronic overdose or misuse, topical corticosteroids should be withdrawn gradually by reducing the frequency of application, or by substituting a less potent corticosteroid, because of the risk of glucocorticosteroid insufficiency.

Consideration should also be given to significant systemic absorption of neomycin sulphate (see *4.4 Special Warnings and Precautions for Use*). If this is suspected, use of the product should be stopped and the patient's general status, hearing acuity, renal and neuromuscular functions should be monitored.

Blood levels of neomycin sulphate should also be determined. Haemodialysis may reduce the serum level of neomycin sulphate.

Further management should be as clinically indicated or as recommended by the National Poisons Centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of action

Betamethasone valerate

Topical corticosteroids act as anti-inflammatory agents via multiple mechanisms to inhibit late phase allergic reactions including decreasing the density of mast cells, decreasing chemotaxis and activation of

eosinophils, decreasing cytokine production by lymphocytes, monocytes, mast cells and eosinophils, and inhibiting the metabolism of arachidonic acid.

Neomycin sulphate

Neomycin interferes with bacterial protein synthesis by binding to 30S ribosomal subunits.

5.2. Pharmacodynamic Properties

ATC code

D07CC01 Corticosteroids, potent, combinations with antibiotics - Betamethasone and antibiotics

Betamethasone valerate

Topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties.

Neomycin sulphate

Neomycin has a bactericidal action against many Gram-negative bacteria but it lacks activity against *Pseudomonas aeruginosa*. It has partial activity against Gram-positive bacteria. It is used topically in the treatment of infections of the skin, ear, and eye due to susceptible staphylococci and other organisms.

5.3. Pharmacokinetic Properties

Absorption

Betamethasone valerate

Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary due to the fact that circulating levels are well below the level of detection.

Neomycin sulphate

Absorption of neomycin has been reported to occur from wounds and inflamed skin. It is poorly absorbed from the gastrointestinal tract when administered orally.

Distribution

Neomycin sulphate

Absorbed neomycin distributes to tissues and concentrates in the renal cortex.

Metabolism

Betamethasone valerate

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolised, primarily in the liver.

Elimination

Betamethasone valerate

Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Neomycin sulphate

Absorbed neomycin is rapidly excreted by the kidneys as parent compound. It has been reported to have a half-life of 2 to 3 hours.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Non-clinical studies have not been conducted with *BETNOVATE-N*.

Betamethasone valerate and neomycin sulphate individually have been evaluated in animal toxicity tests, and the following statements reflect the information available on the individual components

Genotoxicity

Neomycin was negative in the Ames test, HGPRT mutation assay in Chinese hamster ovary (CHO) cells and mouse bone marrow micronucleus test.

Pregnancy

Subcutaneous administration of betamethasone 17-valerate to mice or rats at doses ≥ 0.1 mg/kg/day or rabbits at doses ≥ 12 micrograms/kg/day during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

7. DESCRIPTION

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Neomycin Sulphate I.P. 0.5% w/w
Chlorocresol I.P. 0.1% w/w (as preservative) in a non-greasy base

List of Excipients

Chlorocresol (as preservative)
Cetomacrogol 1000
Cetostearyl alcohol
White soft paraffin
Liquid paraffin
Sodium dihydrogen phosphate dihydrate

Phosphoric acid or sodium hydroxide (for pH adjustment)
Purified water

For important information about some of these excipients see *4.4 Special Warnings and Precautions for Use.*

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

No incompatibilities have been identified

8.2. Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Aluminium collapsible tube in a carton
All presentations may not be marketed in India.

8.4. Storage and Handling Instructions

Store at a temperature not exceeding 25°C.
Do not freeze.

Keep out of reach of children.

Do not dilute.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or their patient's parents) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *BETNOVATE-N*. Patients (and/or their patient's parents) may also be informed about posology, method of administration and storage/handling information as applicable..

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited,
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing Licence number is indicated on the label and packaging.

12. DATE OF REVISION

18 Sep 2020

Trade marks are owned by or licensed to the GSK group of companies.

Version: BEVN/PI/IN/2020/01

Adapted from BETNOVATE GDS 12/ IPI 06 dated 19 May 2020