



BETNOVATE-N cream

QUALITATIVE AND QUANTITATIVE COMPOSITION

BETNOVATE-N cream contains 0.1% w/w betamethasone as the valerate ester and 0.5% w/w neomycin sulfate

PHARMACEUTICAL FORM

Smooth white to off-white cream

CLINICAL PARTICULARS

Indications

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

Topical preparations combining betamethasone valerate and neomycin sulfate 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 bites reactions
- Miliaria (prickly heat)
- Anal and genital intertrigo
- Otitis externa (*see Contraindications*)

Dosage and 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 sulfate 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 cream 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 7 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 cream 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 cream is contraindicated in neonate and infant (less than 2 years) (*see 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 cream 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 Warnings and Precautions*)

Contraindications

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

Due to the known ototoxic and nephrotoxic potential of neomycin sulfate, the use of BETNOVATE-N cream in large quantities or on large areas for prolonged periods of time is contraindicated in circumstances where significant systemic absorption may occur. (*see Dosage and Administration*)

The following conditions should not be treated with BETNOVATE-N cream:

- 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

Warnings and Precautions

Hypersensitivity

BETNOVATE-N cream 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 Adverse Reactions*) 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 cream. 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 Adverse Reactions*).

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 Adverse Reactions*). 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 cream 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 Contraindications*).

Renal impairment

In renal impairment the plasma clearance of neomycin is reduced (*see Dosage and 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 contains 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.

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 sulfate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents.

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

Pregnancy and Lactation

Fertility

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

Pregnancy

There are limited data from the use of BETNOVATE-N cream in pregnant women. Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (*see Pre-Clinical Safety Data*). The relevance of this finding to human 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 Pre-Clinical Safety Data*). Thus use of BETNOVATE-N cream is not recommended in pregnancy.

Lactation

The safe use of BETNOVATE-N cream 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 cream is not recommended in lactation.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of BETNOVATE-N cream 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 cream.

Adverse Reactions

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($\geq 1/10,000$ 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 Warnings and Precautions*), 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.*

Overdose**Symptoms and Signs**

Topically applied BETNOVATE-N cream 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 Adverse Reactions*).

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 sulfate (*see Warnings and Precautions*). 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 sulfate should also be determined. Haemodialysis may reduce the serum level of neomycin sulfate.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

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

Mechanism of action

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

Pharmacodynamic effects

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.

Pharmacokinetics

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 metabolized, 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.

Pre-Clinical Safety Data

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

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

Genotoxicity

Neomycin sulfate

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

Pregnancy

Betamethasone 17-valerate

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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Chlorocresol, Sodium dihydrogen phosphate Dihydrate, Cetomacrogol 1000, Liquid paraffin, Cetostearyl alcohol, White soft paraffin, Phosphoric acid, Sodium hydroxide, Purified water.

For important information about some of these excipients see Warnings and Precautions.

Shelf Life

The expiry date is indicated on the packaging.

Storage

Store below 30°C.

Nature and Contents of Container

BETNOVATE-N cream is packed in a collapsible aluminium tube, internally coated with an epoxy resin based lacquer and closed with a cap.

Instructions for Use/Handling

Do not dilute.

Thai FDA Mandatory Warning

Do not use in patients with known hypersensitivity to this medicine.

Not all presentations are available in every country.

MARKETING AUTHORIZATION HOLDER

GLAXOSMITHKLINE (THAILAND) LTD.

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