Betnovate-N Cream

Presentation
The Betnovate-N Cream contain Betamethasone 0.1% w/w (as betamethasone valerate) and Neomycin Sulphate 0.5% w/w.
Betnovate-N Cream is a smooth, white, water-miscible cream.

Indications
Betnovate-N Cream are indicated for the treatment of the following conditions where secondary bacterial infection is present, suspected, or likely to occur:
Eczema in adults and children (aged 2 years and over), including atopic and discoid eczemas; prurigo nodularis; psoriasis (excluding widespread plaque psoriasis); neurodermatoses including, lichen planus; seborrhoeic dermatitis; contact sensitivity reactions.
Betnovate-N Cream can also be used in the management of insect bites reactions, prickly heat, anal and genital intertrigo.

Dosage and Administration
Betnovate-N Cream is especially appropriate for moist or weeping surfaces. In adults, 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 cases, thereafter improvement can usually be maintained by regular application without occlusion.
Treatment should not be continued for more than 7 days without medical supervision.
When the product is used on the face, the treatment should not be longer than 5 days and occlusive dressing should not be applied.

<u>Adults and children aged 2 years and over:</u>
A small quantity should be applied to the affected area two or three times daily until improvement occurs. It may then be possible to maintain improvement by applying once a day or even less often.
Betnovate-N is suitable for use in children (2 years and over) at the same dose as adults. When used in children, courses should be limited to 5 days, if possible.
A possibility of increased absorption exists in very young children, thus Betnovate-N is not recommended for use in neonates and infants younger than 2 years of age (see Contra-indications).

<u>Dosage in renal/hepatic impairment:</u>
In case of systemic absorption and the development of systemic reactions (when the product is applied over a large surface area for a prolonged period), the metabolism and elimination may be delayed, thus increasing the risk of systemic toxicity. Consequently, the minimum recommended dose should be used for the shortest duration necessary to treat the disease. (see Special Warnings and Precautions for Use).

<u>Elderly:</u>
Betnovate-N is suitable for use in the elderly. Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of neomycin sulphate may occur (see Special Warnings and Precautions for Use).
For topical administration.

Contra-indications
Use in children below 2 years of age.

Rosacea.
Acne vulgaris.
Perioral dermatitis.
Perianal and genital pruritus.
Pruritus without inflammation.
Viral skin 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 with tympanic membrane perforation (risk of ototoxicity in the case of using medicinal products containing neomycin).
Long-term use at high doses or over a large surface of the skin (risk of ototoxicity and nephrotoxicity due to neomycin sulphate as significant systemic absorption may occur)

Special Warnings and Precautions for Use

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 of Betnovate N cream. Local hypersensitivity reactions (see Undesirable effects) may resemble symptoms of the condition under treatment.

Pseudomembranous colitis

Cases of mild to life-threatening pseudomembranous colitis have been reported in patients using antibiotics. Therefore, it is important to consider this diagnosis in patients developing diarrhoea during or after treatment with antibiotics. This is less likely to occur in the case of topical use of the medicinal product; however, if the patient has severe, persistent diarrhoea or experiences abdominal pain, the treatment should be discontinued immediately and the patient should undergo further diagnostic work-up.

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression

Long-term treatment with Betnovate N cream should be avoided where possible, particularly in children, due to the risk of reversible suppression of the HPA axis function and the occurrence of symptoms of Cushing's syndrome resulting from increased corticosteroid absorption. If these symptoms develop, the medicinal product should be discontinued gradually, or less potent corticosteroid should be used. Abrupt treatment withdrawal may result in glucocorticosteroid insufficiency (see Undesirable effects).

Risk factors for increased corticosteroidal systemic effects are:

- High potency and formulation of topical steroid
- Long-term exposure
- Application to a large surface area of the body
- Use on occluded areas of skin (e.g. on intertriginous areas or under occlusive dressings or nappies – in small children, nappies may act as an occlusive dressing),
- Increased hydration of the stratum corneum,
- Use on thin skin areas, e.g. the face

- Use on broken skin or other conditions where the skin barrier may be impaired.

Children

In comparison with adults, children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. Long-term corticosteroid therapy should be avoided in children younger than 12 years due to the risk of HPA axis suppression.

Psoriasis

Topical corticosteroids may have negative effects in psoriasis due to the risk of tolerance to the medicinal product, the risk of lesion worsening resulting from so-called rebounds once the product is discontinued, the risk of generalized pustular psoriasis, the risk of local or systemic toxicity associated with impaired barrier function of the skin (see Undesirable effects), and the risk of local or systemic adverse reactions of corticosteroids, resulting from excessive absorption of the medicinal product through damaged skin.
The use of Betnovate N cream in the treatment of psoriasis should be supervised by a doctor.

Medicinal product dilution

Antimicrobial medicinal products should not be diluted.

Hypersensitivity at the administration site

Prolonged or frequent use of Betnovate N cream may increase the risk of skin hypersensitivity at the application site.

Ototoxicity and nephrotoxicity

Due to systemic absorption, aminoglycoside antibiotics, such as neomycin, may cause irreversible ototoxicity. Neomycin may have nephrotoxic effects (see Contraindications).

Renal impairment

In patients with renal impairment, the serum clearance of neomycin is decreased (see Dosage and Administration).

Application to the face

The face, more than other areas of the body, may exhibit atrophic changes after treatment with topical corticosteroids. This must be taken into consideration, particularly when treating psoriasis, lupus and severe eczema

Application to the eyelids

Ensure that the product does not come into contact with the eyes and mucous membranes. Avoid applying the product to the eyelids as cataract and glaucoma may develop if the product enters conjunctival sac.

Visual disturbance

Visual disturbance may occur 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 chorioretinophathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Infections

Skin infection may persist due to the masking effect of the corticosteroid. In case of secondary infection of inflammatory lesions treated with Betnovate N cream, the corticosteroid should be discontinued and an agent with general antimicrobial properties should be administered.

Risk of bacterial infections under occlusive dressing

Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings.
When the medicinal product is used under occlusive dressings, the skin should be cleansed before a dressing is applied as bacterial infection is encouraged by the warm, moist conditions caused by occlusive dressings.

Leg ulcers

Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher incidence of local hypersensitivity reactions and an increased risk of local infection.
If the patient develops irritation or hypersensitivity reactions, the medicinal product should be discontinued.

Betnovate N Cream contains cetostearyl alcohol, chlorocresol and paraffin

Due to the content of cetostearyl alcohol, the medicinal product may cause a local skin reaction (e.g. contact dermatitis).
Due to the content of chlorocresol, the medicinal product may cause allergic reactions.
Betnovate N cream contains paraffin. Patients should be instructed not to smoke or approach 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 with other medicinal products and other forms of interaction
Concomitant administration with medicinal products that inhibit CYP3A4 (e.g. ritonavir, itraconazole) may inhibit the metabolism of corticosteroids, leading to their increased systemic absorption. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and on the potency of the CYP3A4 inhibitor.
Due to extensive systemic absorption, neomycin sulphate may increase and prolong respiratory system depression caused by depolarizing muscle relaxants.
Concomitant use of topical neomycin sulphate and systemic aminoglycosides may result in accumulated toxicity.

Fertility, pregnancy and Lactation
This medicinal product is not recommended in pregnant and breast-feeding women.

Pregnancy

Topical administration of corticosteroids to pregnant animals caused abnormalities of foetal development, but the relevance of this finding to use of corticosteroids in humans has not been established.
However, neomycin present in maternal blood may cross the placenta, thus increasing the risk of foetal toxicity. Consequently, the use of Betnovate-N cream is not recommended in pregnant women.

Breast-feeding
The safety of Betnovate N cream has not been determined in breast-feeding women. It is not known whether topical corticosteroids could cause sufficient systemic absorption to result in detectable amounts in breast milk.
Consequently, the use of Betnovate N cream in breast-feeding women is not recommended.

Fertility
No data are available on the effects of Betnovate N cream on human fertility.

Effects on ability to drive and use machines
No effects have been demonstrated.

Undesirable Effects

The adverse reactions listed below are classified by MedDRA System Organ Class and frequency defined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1,000) and very rare (<1/10,000), including isolated reports. Information on very common, common and uncommon adverse reactions has been determined mainly based on clinical trial data. Information on rare and very rare adverse reactions has been determined from spontaneous reporting.

Infections and infestations
Very rare: opportunistic infections
Immune system disorders
Very rare: local hypersensitivity
Endocrine disorders
Very rare: HPA axis suppression (see also section “Skin and subcutaneous tissue disorders”), Cushingoid features (e.g. moon face, central obesity), delayed bone growth in children, osteoporosis, glaucoma, hyperglycaemia/glycosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels
Eye disorders
Not known: Blurred vision (see Special Warnings and Precautions for Use)
Skin and subcutaneous tissue disorders
Common: local skin burning/pain and pruritus
Very rare: skin thinning*/atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasia*, pigmentation changes*, hypertrichosis, alopecia*, trichorrhexis nodosa*, exacerbation of disease symptoms, allergic contact dermatitis/dermatitis, erythema, rash, urticarial, pustular psoriasis (See Special warnings and precautions for use)
*Symptoms of HPA axis suppression.

Due to the content of a potent corticosteroid, long-term use of the medicinal product may result in local atrophic lesion, such as skin thinning, striae and telangiectasia, especially when used in skin folds or with occlusion.

General disorders and administration site conditions
Very rare: application site irritation/pain
Betnovate N cream is usually well-tolerated; nevertheless, symptoms of hypersensitivity to ingredients of the medicinal product constitute an indication for immediate treatment discontinuation.

In rare cases, the use (or discontinuation) of the medicinal product in psoriatic patients is associated with the risk of generalized pustular psoriasis.

Overdose
Symptoms
Betnovate N cream applied topically to the skin may be absorbed in sufficient amounts to produce systemic effects. Acute overdose is very unlikely, but in the case of prolonged or incorrect use patients may develop symptoms of Cushing's syndrome (See Undesirable effects).
In addition, large amounts of neomycin sulphate may be absorbed in the body (see Special Warnings and Precautions for Use).

Treatment
In the event of overdose, the medicinal product should be withdrawn gradually by reducing the frequency of application or by substituting Betnovate N cream with a less potent corticosteroid to avoid the risk of glucocorticosteroid insufficiency. Due to the risk of acute adrenal insufficiency, this should be supervised closely by a doctor. Also, consideration should be given to significant systemic absorption of neomycin sulphate (see Special Warnings and Precautions for Use). If the doctor suspects such a situation, the use of Betnovate N cream should be discontinued and the patient's condition should be assessed, including his/her hearing, renal and neuromuscular system functions .
Blood levels of neomycin sulphate also need to be determined. Haemodialysis may reduce the plasma concentration of neomycin sulphate.
Overdose treatment should be supervised by a doctor

Pharmacodynamic properties
Pharmacotherapeutic group: Topical corticosteroids, potent in combination with antibiotics. ATC code: D 07 CC 01.
Betamethasone valerate is a potent topical corticosteroid.
Neomycin sulphate is a multitarget aminoglycoside antibiotic against most bacteria that cause inflammation in the skin.

Pharmacokinetic properties
The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the integrity of the epidermal barrier and occlusive dressing. Topical corticosteroids may be absorbed through healthy, intact skin. Inflammation and/or other skin disease processes increase absorption through the skin. Occlusive dressings significantly increase the percutaneous absorption of topical corticosteroids. Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids bind to proteins with varying degrees and are metabolised mainly in the liver and subsequently excreted by the kidney.

Pre-clinical safety data
No additional data apart from those mentioned in other sections of the summary of product characteristics.

List of Excipients

Chlorocresol, sodium dihydrogen phosphate dihydrate, cetomacrogol 1000, liquid paraffin, cetostearyl alcohol, white soft paraffin, phosphoric acid, sodium hydroxide, purified water

Storage
Store as directed on the outer package.

Use and Handling
Do not dilute.

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