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

BETNOVATE-GM

1. GENERIC NAME

Betamethasone Valerate, Gentamicin and Miconazole Nitrate Skin Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Gentamicin Sulphate I.P. equivalent to Gentamicin 0.10 % w/w
Miconazole Nitrate I.P. 2.0 % w/w
Chlorocresol I.P. 0.1 % w/w (as preservative) in a non-greasy base

3. DOSAGE FORM AND STRENGTH

Cream

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BETNOVATE-GM is indicated for steroid responsive dermatosis associated with mixed infection.

4.2 Posology and Method of Administration

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

BETNOVATE-GM should not be used continuously for more than one week without re-evaluation by the physician.

Adults and adolescents

Apply thinly and gently rub in using only enough to cover the entire affected area twice daily for up to seven days, then change to another corticosteroid preparation not containing gentamicin 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 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-GM 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-GM* is contraindicated in children under 2 years of age (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-GM* to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

BETNOVATE-GM is suitable for use in the elderly. However, the greater frequency of decreased hepatic and 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-GM cream is contraindicated in children under 2 years of age.

Due to the known ototoxic and nephrotoxic potential of gentamicin sulphate, the use of *BETNOVATE-GM* cream 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-GM:*

- 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, bacteria, or yeast
- Otitis externa when the ear drum is perforated, because of the risk of ototoxicity

4.4 Special Warnings and Precautions for Use

Hypersensitivity

BETNOVATE-GM cream should be used with caution in patients with a history of local hypersensitivity to betamethasone, gentamicin, miconazole 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.

Application to open wounds should be avoided.

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-GM.* 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 corticosteroid 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 disturbance

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 may increase the risk of contact sensitisation.

Ototoxicity and nephrotoxicity

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

Renal impairment

In renal impairment the plasma clearance of gentamicin 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 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 (see *4.8 Undesirable Effects*). In case of accidental contact with the eyes or mucous membranes, rinse with water.

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 and 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

Product 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.

4.5 Drug Interactions

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir and 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, gentamicin sulphate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents.

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

It is known that systemically administered miconazole nitrate inhibits CYP3A4/2C9. As there is limited percutaneous absorption of miconazole, topical application is not expected to result in systemic exposure of clinical significance. However, as there have been case reports of topical or intravaginal miconazole cream potentiating the anticoagulant effects of coumarins in adults, caution should be exercised with concomitant use and anticoagulant effect monitored.

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

Fertility

There are no data in humans to evaluate the effect of topical betamethasone valerate with gentamicin on fertility.

No fertility studies in animals have been performed with topical miconazole. Animal studies indicate no effects of oral miconazole on male or female fertility (*see 6 Nonclinical properties*). As there is limited percutaneous absorption of miconazole following topical application, impact on fertility is not expected.

Pregnancy

There are limited data from the use of topical betamethasone valerate with gentamicin in pregnant women.

There are no adequate and well-controlled studies of topical miconazole in pregnant women. Oral miconazole has been shown to be embryotoxic in the rat at high doses (*see 6 Nonclinical properties).* No reproductive studies in animals have been performed with topical miconazole.

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, gentamicin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity. Thus the use of *BETNOVATE-GM* is not recommended in pregnancy.

Lactation

Percutaneous absorption of miconazole is limited, however, it is not known whether miconazole is excreted in human milk after topical application.

The safe use of betamethasone valerate with gentamicin and miconazole 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-GM* 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 betamethasone valerate with gentamicin on driving performance or the ability to operate machinery. Miconazole is not known to exert an effect on the central nervous system following topical application. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of *BETNOVATE-GM*.

4.8 Undesirable Effects

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

Rare	Application site 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, skin burning sensation/skin pain
Rare	Blister, dermatitis, skin irritation (including dry skin and erythema), rash and skin discoloration
Very rare	Allergic contact dermatitis, urticaria, pustular psoriasis (*see also 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*

**Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.*

General Disorders and Administration Site Conditions

Rare	Application site irritation/pain

4.9 Overdose

Symptoms and signs

Topically applied betamethasone valerate and gentamicin sulphate 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, *BETNOVATE-GM* 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 be given to significant systemic absorption of gentamicin sulphate *(*see *4.4 Special Warnings and Precautions for Use, 4.5 Drug Interactions).* 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 gentamicin sulphate should also be determined. Haemodialysis may reduce the serum level of gentamicin sulphate.
Further management should be as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic Properties

Betamethasone valerate

Absorption

Topical corticosteroids can be systematically 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.

Distribution

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.

Metabolism

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

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

Gentamicin sulphate

Absorption

Topical application of gentamicin can result in some systemic absorption, particularly from wounds and inflamed skin.

Distribution

Absorbed gentamicin distributes to tissues. Aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney.

Metabolism and Elimination

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration.

Miconazole nitrate

There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.

Distribution

Absorbed miconazole is distributed systematically and over 90% is bound to the plasma proteins, primarily albumin.

Metabolism and Elimination

Miconazole nitrate is highly metabolised in humans. Following oral administration, approximately 18% of an administered dose was excreted in the urine; most of it consisted of metabolites and less than 1% was accounted for as unchanged miconazole. Approximately 50% or more of the administered dose was recovered from the faeces, mostly as unchanged drug.

5.3 Pharmacodynamic Properties

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.

Gentamicin sulphate

Gentamicin is mixture of antibiotic substances produced by the growth of *Micromonospora Purpurea*. It is a bactericidal antibiotic which acts by inhibiting protein synthesis. It has greater antibacterial activity than streptomycin, neomycin or kanamycin.

Gentamicin exerts a number of effects on cells of susceptible bacteria. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effect is inhibition of protein synthesis at the level of the 30s ribosomal subunit.

Miconazole Nitrate

Miconazole nitrate is an imidazole antifungal agent and may act by interfering with the permeability of the fungal cell membrane. It possesses a wide antifungal spectrum and has some antibacterial activity.

6. NONCLINICAL PROPERTIES

Non-clinical studies have not been conducted with Betamethasone valerate with gentamicin and miconazole.

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

There is no pre-clinical data of relevance for gentamicin which are additional to that already included in other sections of the prescribing information.

Carcinogenesis

Miconazole nitrate was negative in a bacterial reverse mutation test, a chromosome aberration test in mice, and micronucleus assays in mice and rats.

Fertility

The effect on fertility of betamethasone valerate has not been evaluated in animals.

Miconazole nitrate had no adverse effect on fertility in a study in male and female rats at oral doses of up to 320 mg/kg/day.

Pregnancy

Subcutaneous administration of betamethasone 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.

In studies performed in rats and rabbits, oral miconazole was not teratogenic, however miconazole is embryotoxic in the rat at high doses. Miconazole nitrate administration has been shown to result in prolonged gestation and decreased numbers of live young in rats and in increased number of resorptions and decreased number of live young in rabbits at oral doses of 100 mg/kg/day and 80 mg/kg/day.

7. DESCRIPTION

Cream

Contains:
Betamethasone Valerate I.P. equivalent to Betamethasone 0.10 % w/w
Gentamicin Sulphate I.P. equivalent to Gentamicin 0.10 % w/w
Miconazole Nitrate I.P. 2.0 % w/w
Chlorocresol I.P. 0.1 % w/w (as preservative) in a non-greasy base

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Chlorocresol (as preservative), Cetomacrogol 1000, Cetosteryl alcohol, White soft paraffin, Liquid paraffin, Sodium citrate, Citric acid monohydrate, Propylene glycol, Purified water

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 tube in a carton

8.4 Storage and Handling Instructions

Store at temperature below 25ºC. Do not freeze.

Keep out of reach of children.

For external use only.

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-GM*. 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 License number is indicated on the label and packaging.

12. DATE OF REVISION

24-SEP-2020

Version: BEV-GM/PI/IN/2020/02

Adapted from

- *Betamethasone 17 valerate – Neomycin sulphate GDS Version 12 dated 19 May 2020*
- *Miconazole GDS Version 03 dated 23 August 2013*
- *Betamethasone 17 valerate (topical) (BETNOVATE) GDS 10 dated 11 Jun 2020*
- *Gentamicin 0.3% w/v and Hydrocortisone acetate 1% w/v Ear Drops SPC (Gentisone HC Ear Drops) updated on eMC 23-Aug-2019 (ADVANZ Pharma), date of revision of the text 14-Aug-2019*
- *Miconazole Nitrate (Daktarin 2% Cream) SPC updated on eMC 26 Aug 2020 (McNeil Products Ltd.), date of revision of the text 04 Sep 2020*