

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

EUMOSONEM

1. GENERIC NAME

Clobetasone Butyrate and Miconazole Nitrate Skin Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clobetasone Butyrate IP	0.05 % w/w
Miconazole Nitrate IP	2.0 % w/w
Chlorocresol IP (As Preservative) in a non greasy base	0.1 % w/w

3. DOSAGE FORM AND STRENGTH

Cream

EUMOSONEM contains:

Clobetasone Butyrate IP	0.05 % w/w
Miconazole Nitrate IP	2.0 % w/w
Chlorocresol IP (As Preservative) in a non greasy base	0.1 % w/w

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clobetasone butyrate is a moderately potent topical corticosteroid indicated for adults, elderly, children and infants for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses. Miconazole nitrate is an imidazole antifungal agent.

Topical preparations combining clobetasone with miconazole are indicated for the treatment and management of steroid responsive dermatoses where secondary fungal infection is present, suspected or likely to occur.

These include the following: atopic dermatitis, nappy rash, intertrigo, seborrhoeic dermatitis.

4.2 Posology and Method of Administration

Adults, Elderly, Children and Infants

Creams are especially appropriate for moist or weeping surfaces.

Apply thinly and gently rub in using only enough to cover the entire affected area twice a day for up to seven days. If the infection worsens, treatment and diagnosis should be re-evaluated as soon as possible.

If the condition does not improve within seven days, treatment and diagnosis should be re-evaluated.

Treatment should not be continued for more than seven days without medical supervision.

Allow adequate time for absorption after each application before applying an emollient. Patients should be advised to wash their hands after applying clobetasone with miconazole, unless it is the hands that are being treated.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroids especially with potent preparations. If further treatment is required to achieve control of the pre-existing dermatoses, it may be necessary to continue therapy with another corticosteroid preparation not containing miconazole.

Children

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

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

Elderly

Clinical studies of clobetasone butyrate have not identified differences 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/Hepatic Impairment

In case of systemic absorption (when application is over a large surface area for a prolonged period), metabolism and elimination may be delayed therefore increasing the risk of systemic toxicity. Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

4.3 Contraindications

EUMOSONE M is contra-indicated in untreated primary cutaneous infections, secondary bacterial and viral cutaneous infections, rosacea, acne vulgaris, pruritus without inflammation and in people with history of hypersensitivity to any ingredient in the product or to other imidazole derivatives.

4.4 Special Warnings and Precautions for Use

Local hypersensitivity reactions (see *4.8 Undesirable Effects*) may resemble symptoms of the condition under treatment.

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with other miconazole topical formulations (see *4.8 Undesirable Effects*). If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued.

Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency can occur in some individuals as a result of increased systemic absorption of topical steroids. 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 systemic effects are:

- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (in infants the nappy 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
- In comparison with adults, children and infants 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.

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.

Children

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression is more likely to occur.

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.

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.

Concomitant bacterial and/or viral infection

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have bacterial and /or viral infection also. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate antimicrobial therapy.

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.

Accidental ingestion

For external use only. This and all medication should be kept out of the reach of children. In case of accidental ingestion, professional assistance should be sought (see 4.9 *Overdose*).

Infection

Extension of the infection may occur due to the masking effect of the corticosteroid. If infection persists, systemic chemotherapy may be required. Any spread of infection requires withdrawal of topical corticosteroid therapy.

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.

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after topical application, clinically relevant interactions are rare. However, in patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored.

4.6 Use in Special Populations

Fertility

There are no data in humans to evaluate the effect of topical corticosteroids on fertility

Pregnancy

There are limited data from the use of clobetasone 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.

In animals miconazole nitrate has shown no teratogenic effects but is fetotoxic at high oral doses. Only small amounts of miconazole nitrate are absorbed following topical administration.

Therefore, administration of *EUMOSONEM* during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus. The minimum quantity should be used for the minimum duration.

Lactation

The safe use of topical corticosteroids during lactation has not been established.

It is not known whether the topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk.

Topically applied miconazole is minimally absorbed into the systemic circulation, and it is not known whether miconazole is excreted in human breast milk.

Administration of *EUMOSONEM* during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

If used during lactation, *EUMOSONEM* should not be applied to the breasts to avoid accidental ingestion by the infant.

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *EUMOSONEM* 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 active ingredients of *EUMOSONEM*.

4.8 Undesirable Effects

In absence of availability of adverse event data on the fixed dose combination of clobetasone butyrate and miconazole nitrate, adverse event data of the individual ingredients is presented below.

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.

Clobetasone butyrate

Post-Marketing Data

Infections and Infestations

Very rare Opportunistic infection

Immune System Disorders

Very rare Hypersensitivity

Endocrine Disorders

Very rare Hypothalamic-pituitary adrenal (HPA) axis suppression:

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

Very rare Allergic contact dermatitis, urticaria, skin atrophy*, pigmentation changes*, exacerbation of underlying symptoms, local skin burning, hypertrichosis, rash, pruritus, erythema

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

Miconazole nitrate

Adverse drug reactions reported among 834 patients who received miconazole nitrate 2% cream (n=426) and/or placebo cream base (n=408) in 21 double-blind clinical trials are presented in Table 1 below. Moreover, adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with miconazole nitrate 2% cream that meet threshold criteria are included in Table 1.

Adverse reactions obtained from clinical studies and post-marketing surveillance are presented by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 1: Adverse reactions reported in clinical trials and post-marketing experience

<i>Immune System Disorders</i>	
Not known:	Anaphylactic reaction Hypersensitivity

<i>Skin and Subcutaneous Tissue Disorders</i>	
Uncommon:	Skin burning sensation Skin inflammation Skin hypopigmentation
Not known:	Angioedema Urticaria Contact dermatitis Rash Erythema Pruritus

<i>General Disorders and Administration Site Conditions</i>	
Uncommon:	Application site irritation Application site burning Application site pruritus Application site reaction NOS Application site warmth

4.9 Overdose

Symptoms and signs

Topically applied clobetasone butyrate 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*).

Excessive topical use of miconazole nitrate can result in skin irritation, which usually disappears after discontinuation of therapy.

Treatment

In the event of overdose, *EUMOSONE M* should be withdrawn gradually by reducing the frequency of application or by substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency.

Further management should be as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Clobetasone butyrate

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.

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.

5.2 Pharmacodynamic Properties

Clobetasone butyrate

Pharmacotherapeutic classification: Corticosteroids, moderately potent (group II). ATC code: D07AB.

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

Miconazole nitrate

Pharmacotherapeutic classification: Antifungals for dermatological/topical use; imidazole derivative.

ATC code: D01A C02.

5.3 Pharmacokinetic Properties

Absorption

Clobetasone butyrate

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.

Miconazole nitrate

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

Distribution

Clobetasone butyrate

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.

Miconazole nitrate

Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells (10.6%).

Metabolism

Clobetasone butyrate

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

Clobetasone butyrate

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

Miconazole nitrate

The small amount of miconazole that is absorbed is eliminated predominantly in faeces as both unchanged drug and metabolites.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology and Pharmacology

Clobetasone butyrate

Carcinogenesis

Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical clobetasone.

Genotoxicity

Clobetasone was not mutagenic *in vitro* or *in vivo*.

Fertility

The effect on fertility of topical clobetasone has not been evaluated in animals.

Pregnancy

Topical application of clobetasone to rats at doses of 0.5 or 5 mg/kg/day, and subcutaneous administration to mice at doses ≥ 3 mg/kg/day or rabbits at doses ≥ 30 μ g/kg/day during pregnancy resulted in foetal abnormalities including cleft palate.

Miconazole nitrate

Preclinical data on miconazole reveal no special hazard for humans based on conventional studies of local irritation, single and repeated dose toxicity, genotoxicity and toxicity to reproduction.

Also see 4.6 *Use in Special Populations*

7. DESCRIPTION

Cream

EUMOSONE M contains:

Clobetasone Butyrate IP	0.05 % w/w
Miconazole Nitrate IP	2.0 % w/w
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in a non-greasy base

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Glyceryl Monostearate (NSE), Cetostearyl Alcohol, Beeswax white, Arlacel 165, Dimethic one 20, Glycerin, Chlorocresol, Sodium citrate, Citric acid, 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

Tube in a carton.

8.4 Storage and Handling Information

For external use only.

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

Keep out of reach of children.

There are no special requirements for use or handling of this product.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients and/or their patients' parents about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *EUMOSONE M*. Patients 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

28-Oct-19

Trademarks are owned by or licensed to the GSK group of companies

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Adapted from:

- *Clobetasone butyrate (topical) GDS 10/IPI 04 dated 09-April-2018*
- *Summary of Product Characteristics (SPC) of Miconazole Nitrate (Daktarin 2% Cream - McNeil Products Ltd.) updated 25-Aug-2016 on eMC, date of revision of text 08 Aug 2016*
- *Summary of Product Characteristics (SmPC) of Trimovate updated 17-Oct-18 on eMC, date of revision of text 23 Nov 17*