EUMOSONE M

Clobetasone Butyrate and Miconazole Nitrate Skin Cream

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

PHARMACEUTICAL FORM

Cream

CLINICAL PARTICULARS

Therapeutic Indications

EUMOSONE-M is a combination of a moderately potent topical corticosteroid and topical antifungal agent and is indicated for the treatment of the following conditions where secondary fungal infection is present, suspected or likely to occur: atopic dermatitis, irritant or allergic contact dermatitis, seborrhoeic dermatitis, nappy rash, photodermatitis, otitis externa, prurigo nodularis and insect bite reactions.

Posology and Method of Administration

Creams are especially appropriate for moist or weeping surfaces.

Adults and adolescents

Atopic dermatitis (eczema)

Apply thinly and gently rub in using only enough to cover the entire affected area twice daily until improvement occurs, then reduce the frequency of application or change the treatment to a less potent preparation. Allow adequate time for absorption after each application before applying an emollient.

If the condition worsens or does not improve within four weeks, treatment and diagnosis should be re-evaluated.

Therapy with topical corticosteroids should be gradually discontinued once control is achieved and an emollient continued as maintenance therapy.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroids especially with potent preparations.
**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 *EUMOSONE-M* 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.

**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.

**Special Warnings and Special Precautions for Use**

*EUMOSONE-M* should be used with caution in patients with a history of local hypersensitivity to corticosteroids or to any of the excipients in the preparation. Local hypersensitivity reactions (see 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 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 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 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.

**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.

*EUMOSONE M* must not come into contact with the mucosa of the eyes.

**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 or a national poison control centre contacted immediately (see *Overdose*).

**Persistent infection**

If infection persists, systemic chemotherapy is required.

**Interactions with Other Medicaments and Other Forms of 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.

**Pregnancy & Lactation**

**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 *Preclinical Safety Data*).

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 *EUMOSONE-M* 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 *EUMOSONE-M* during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

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

**Effects on Ability to Drive and Use Machines**

There have been no studies to investigate the effect of *EUMOSONE-M* 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 clobetasone butyrate and miconazole nitrate.

**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.

**Post-Marketing Data**

**Clobetasone butyrate**

*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**

**Immune system disorders**

Not known  Anaphylactic reaction, hypersensitivity

**Skin and subcutaneous tissue disorders**

Uncommon  Skin burning sensation, skin inflammation, skin hypopigmentation

Not known  Angioedema, urticaria, contact dermatitis, rash, erythema, pruritus

**General disorders and administration site conditions**

Uncommon  Application site irritation, application site burning, application site pruritus, application site reaction NOS, application site warmth

**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 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 or as recommended by the national poisons centre, where available.

**PHARMACOLOGICAL PROPERTIES**

 **Pharmacodynamic Properties**
**Clobetasone butyrate**

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

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.

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

**Miconazole nitrate**

Pharmacotherapeutic classification: Antifungals for dermatological/topical use; imidazole derivative; ATC code: D01A C02.

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.

**Pharmacokinetic Properties**

**Absorption**

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 when applied topically has very little absorption through skin or mucous membrane.

**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.

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

**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.

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

**Preclinical Safety Data**

**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 µgs/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 *Pregnancy and Lactation*

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**

Glyceryl Monostearate, Cetostearyl Alcohol, Beeswax white, Arlacel 165, Dimethicone 20, Glycerin, Chlorocresol, Sodium citrate, Citric acid, Purified Water.

**Incompatibilities**

No incompatibilities have been identified.

**Shelf Life**

The expiry date is indicated on the label and packaging.
**Special Precautions for Storage**

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

Keep out of reach of children.

**Nature and Specification of Container**

Tube in a carton.

**Instructions for Use / Handling**

For external use only.

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

**For further information please contact:**

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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