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Eumovate Cream

1. Name of the Medicinal Product

Eumovate Cream

2. Qualitative and Quantitative Composition

0.05% w/w clobetasone butyrate.

Excipients with known effect:
Cetostearyl alcohol
Chlorocresol

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Cream.

Clinical Particulars

4.1 Therapeutic Indications

Topical treatment for corticosteroids responsive dermatosis

4.2 Posology and Method of Administration

Route of administration: Cutaneous

Adults, Elderly, Children and Infants from the age of 3 month
Creams are especially appropriate for moist or weeping surfaces.

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice a day 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.

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.

Duration of treatment for adults and elderly
Continuous daily treatment for longer than four weeks is not recommended. If the condition worsens or does not improve within four weeks, treatment and diagnosis should be re-evaluated.

Paediatric population

Use in children under 12 years should be on the advice of a doctor.

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

Duration of treatment for children and infants
When clobetasone is used in the treatment of dermatoses in children, extreme caution is required and treatment should not normally exceed 7 days.
If the condition worsens or does not improve within 7 days, treatment should be reviewed.

Once the condition has been controlled, the frequency of application should be reduced to the lowest effective dose for the shortest time possible.

Continuous daily treatment for longer than 4 weeks is not recommended in children

Elderly
Clinical studies 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 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

The following conditions should not be treated with Eumovate:

- Untreated cutaneous infections.
- Rosacea
- Acne vulgaris
- Pruritus without inflammation.

4.4 Special Warnings and Precautions for Use

Eumovate should be used with caution in patients with a history of local hypersensitivity to **other** corticosteroids. Local hypersensitivity reactions (*see section 4.8*) may resemble symptoms of the condition under treatment.

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 (s*ee section 4.8).*

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 can be considered 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.

Paediatric population

Children are more likely to develop local and systemic adverse reactions due to the use of local corticosteroids because of their higher surface area to body mass ratio and, in general, require a shorter treatment.

Particularly, in infants and toddlers the nappy can be considered as an occlusive dressing and therefore can enhance absorption.

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal and growth 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.

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

Concomitant infection
Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. 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 (s*ee section 4.9*).

Eumovate Cream contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis) and chlorocresol which may cause allergic reactions.

4.5 Interactions with other Medicaments and other forms of Interaction

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.

4.6 Fertility, pregnancy and lactation

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 section 5.3).
The relevance of this finding to humans has not been established. Administration of clobetasone 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.

Breast-feeding
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. Administration of clobetasone during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.
If used during lactation, clobetasone should not be applied to the breasts to avoid accidental ingestion by the infant.

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

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of clobetasone 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.

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.

Post-marketing data

Infections and Infestations

Very rare	Opportunistic infection

Immune System Disorders

Very rare	Hypersensitivity, generalised rash

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.*

Eye disorders

Not known	Vision, blurred (see also section 4.4)

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il). Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Symptoms and signs
Topically applied clobetasone 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 section 4.8*).

Treatment
In the event of overdose, clobetasone 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

5.1 Pharmacodynamic Properties

ATC code

D07AB Corticosteroids, moderately potent (group II)

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.

Pharmacodynamic effects
Topical corticosteroids, have anti-inflammatory, antipruritic and vasoconstrictive properties.
Clobetasone butyrate has little effect on hypothalamo-pituitary-adrenal function. This was so even when Eumovate was applied to adults in large amounts under whole body occlusion.

Clobetasone butyrate is less potent than other available corticosteroid preparations and has been shown not to suppress the hypothalamo-pituitary-adrenal axis in patients treated for psoriasis or eczema.

Pharmacological studies in man and animals have shown that clobetasone butyrate has a relatively high level of topical activity accompanied by a low level of systemic activity.

5.2 Pharmacokinetic Properties

Absorption and Distribution
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.

A single application of 30g clobetasone butyrate 0.05% ointment to eight patients resulted in a measurable rise in plasma clobetasone butyrate levels during the first three hours but then the levels gradually decreased. The maximum plasma level reached in the first three hours was 0.6ng/ml. This rise in levels was followed by a more gradual decline with plasma levels of clobetasone butyrate falling below 0.1ng/ml (the lower limit of the assay) after 72 hours. The normal diurnal variation in plasma cortisol levels was not affected by the application of clobetasone butyrate ointment.

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.

5.3 Preclinical Safety Data

Genotoxicity and Carcinogenesis
Conventional *in vitro* and *in vivo* genotoxicity studies reveal no hazard for humans. Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical clobetasone.

Reproductive toxicity
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 µg/kg/day during pregnancy resulted in foetal abnormalities including cleft palate, intrauterine growth retardation and foetal loss.

Pharmaceutical Particulars

6.1 List of Excipients

Glycerol
Glycerol monostearate
Cetostearyl alcohol
Beeswax substitute 6621
Arlacel 165
Dimeticone 20
Chlorocresol
Sodium citrate
Citric acid monohydrate
Purified water

6.2 Incompatibilities

None stated.

6.3 Shelf Life

The expiry date of the product is indicated on the label and packaging.

Use within 12 weeks after opening.

6.4 Special Precautions for Storage

Store below 25°C.

6.5 Nature and Contents of Container

Internally lacquered aluminium tubes with latex band and wadless polypropylene cap.

25, 30 and 100 gr tubes are available.

6.6 Special precautions for disposal and other handling

Patients should be advised to wash their hands after applying Eumovate, unless it is the hands that are being treated.

7. Manufacturer

Glaxo Operations (UK) Limited, Barnard Castle, UK.

8. License Holder and Importer

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. License Number

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