Prescribing Information/Insert

DERMOVATE™

Clobetasol propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

DERMOVATE Cream and Ointment contains Clobetasol propionate 0.05 % w/w.

PHARMACEUTICAL FORM

Cream and Ointment.

CLINICAL PARTICULARS

Indications

DERMOVATE is a very potent topical corticosteroid indicated for adults, elderly and children over 1 year for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses.

These include the following:

- Psoriasis (excluding widespread plaque psoriasis).
- Recalcitrant dermatoses
- Lichen planus
- Discoid lupus erythematosus
- Other skin conditions which do not respond satisfactorily to less potent steroids

Dosage and Administration

Ointment

Ointments are especially appropriate for dry, lichenified or scaly lesions.

Cream

Creams are especially appropriate for moist or weeping surfaces.

Adults, Elderly and Children over 1 year

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice a day for up to 4 weeks 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.

Repeated short courses of *DERMOVATE* may be used to control exacerbations.

In more resistant lesions, especially where there is hyperkeratosis, the effect of *DERMOVATE* 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. Thereafter improvement can usually be maintained by application without occlusion.

If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated.

Treatment should not be continued for more than 4 weeks. If continuous treatment is necessary, a less potent preparation should be used.

The maximum weekly dose should not exceed 50gms/week.

Atopic dermatitis (eczema)

Therapy with *DERMOVATE* cream and ointment 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 *DERMOVATE*.

Recalcitrant dermatoses

Patients who frequently relapse

Once an acute episode has been treated effectively with a continuous course of topical corticosteroid, intermittent dosing (once daily, twice weekly, without occlusion) may be considered. This has been shown to be helpful in reducing the frequency of relapse.

Application should be continued to all previously affected sites or to known sites of potential relapse. This regime should be combined with routine daily use of emollients. The condition and the benefits and risks of continued treatment must be re-evaluated on a regular basis.

Children

DERMOVATE is contraindicated in children under one year of age.

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 *DERMOVATE* to ensure the amount applied is the minimum that provides therapeutic benefit.

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.

Contraindications

The following conditions should not be treated with *DERMOVATE*

- Untreated cutaneous infections
- Rosacea
- Acne vulgaris
- Pruritus without inflammation.
- Perianal and genital pruritus
- Perioral dermatitis

DERMOVATE is contraindicated in dermatoses in children under one year of age, including dermatitis.

Warnings and Precautions

DERMOVATE 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 Adverse Reactions) 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 (see Adverse Reactions).

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.

Children

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

Children are more susceptible to develop atrophic changes with the use of topical corticosteroids. If *DERMOVATE* is required for use in children, it is recommended that the treatment should be limited to only a few days and reviewed weekly.

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.

Use in psoriasis

Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerances, 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. If used in psoriasis careful patient supervision is important.

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.
Application to the face
Application to the face is undesirable as this area is more susceptible to atrophic changes. If used on the face, treatment should be limited to only a few days.
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.
Interactions
Co-administered drugs that can inhibit CYP3A4 (eg 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.
Pregnancy and Lactation
Fertility
There are no data in humans to evaluate the effect of topical corticosteroids on fertility. Clobetasol administered subcutaneously to rats had no effect upon mating performance; however, fertility was decreased at the highest dose (*see Pre-Clinical Safety Data*).
Pregnancy
There are limited data from the use of *DERMOVATE* in pregnant women.
Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (*see Pre-Clinical Safety Data*).
The relevance of this finding to humans has not been established. Administration of *DERMOVATE* 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. Administration of *DERMOVATE* during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.
If used during lactation *DERMOVATE* 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 *DERMOVATE* 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 *DERMOVATE*.
Adverse Reactions
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 Local 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/glucosuri, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels, alopecia, trichorrhexis.

Skin and Subcutaneous Tissue Disorders

Common Pruritus, local skin burning /skin pain

Uncommon Skin atrophy*, striae*, telangiectasias*

Very rare Skin thinning*, skin wrinkling*, skin dryness*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, allergic contact dermatitis/dermatitis, pustular psoriasis, erythema, rash, urticaria, acne

General Disorders and Administration Site Conditions
Very rare Application site irritation/pain
*Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.
Overdose
Symptoms and signs
Topically applied *DERMOVATE* 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 Adverse Reactions).
Treatment
In the event of overdose, *DERMOVATE* 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
Pharmacodynamics
ATC code
D07AD Corticosteroids, very potent (group IV)
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.
Pharmacokinetics
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.
Mean peak plasma clobetasol propionate concentrations of 0.63 nanograms/ml occurred in one study eight hours after the second application (13 h after an initial application) of 30 g clobetasol propionate 0.05 % ointment to normal individuals with healthy skin. Following the application of a second dose of 30 g clobetasol propionate cream 0.05 %, mean peak plasma concentrations were slightly higher than the ointment and occurred 10 h after application. In a separate study, mean peak plasma concentrations of approximately 2.3 nanograms/ml and 4.6 nanograms/ml occurred respectively in patients with psoriasis and eczema three hours after a single application of 25 g clobetasol propionate 0.05 % ointment.
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.

Pre-clinical Safety Data

Carcinogenesis / Mutagenesis

Carcinogenesis

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

Genotoxicity

Clobetasol propionate was not mutagenic in a range of *in vitro* bacterial cell assays.

Fertility

In fertility studies, subcutaneous administration of clobetasol propionate to rats at doses of 6.25 to 50 micrograms/kg/day produced no effects on mating, and fertility was only decreased at 50 micrograms/kg/day.

Pregnancy

Subcutaneous administration of clobetasol propionate to mice (≥100 micrograms/kg/day), rats (400 micrograms/kg/day) or rabbits (1 to 10 micrograms/kg/day) during pregnancy produced foetal abnormalities including cleft palate.

In the rat study, where some animals were allowed to litter, developmental delay was observed in the F1 generation at ≥100 micrograms/kg/day and survival was reduced at 400 micrograms/kg/day. No treatment-related effects were observed in F1 reproductive performance or in the F2 generation.

PHARMACEUTICAL PARTICULARS

List of Excipients

Cream:

Glyceryl monostearate,Cetostearyl alcohol,Chlorocresol, Sodium citrate, Citric acid (monohydrate), Purified water, Arlacel 165, Beeswax substitute 6621, Propylene glycol.

Ointment:

Propylene glycol, White soft paraffin, Sorbitan sesquioleate.

Incompatibilities

No incompatibilities have been identified.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Cream

Store below 30°C.

Ointment

Store below 25° C or 30° C. The storage conditions depend on the locally registered shelf-life (refer to the pack for information).

Nature and Contents of Container

Cream

Collapsible, aluminium tubes, containing 10 gm tube

Ointment

Collapsible, aluminium tubes, containing 10 gm tube

Instructions for Use/Handling

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

Manufactured by

GlaxoSmithKline Bangladesh Limited,
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