CUTIVATE

Fluticasone-propionate

1. Name of The Medicinal Product

Cutivate Cream

2. Qualitative and Quantitative Composition

Each gram of CUTIVATE Cream 0.05% w/w contains 500 micrograms of fluticasone propionate (micronised).

3. Pharmaceutical Form

Cream

4. Clinical Particulars

4.1 Indications

TREATMENT OF INFLAMMATORY DERMATOSES

CUTIVATE Cream is a potent topical corticosteroid indicated for adults, children and infants aged 3 months and over for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

These include: the following:

- Atopic dermatitis (including infantile atopic dermatitis)
- Nummular dermatitis (discoid eczemas)
- Prurigo nodularis
- Psoriasis(excluding widespread plaque psoriasis)
- Lichen simplex chronicus (neurodermatitis) and lichen planus
- Seborrhoeic dermatitis
- Irritant or allergic contact dermatitis
- Discoid lupus erythematosus

- An adjunct to systemic steroid therapy in generalised erythroderma
- Insect bite reactions
- Miliaria (prickly heat)

Children:

For children and infants aged three months and over who are unresponsive to lower potency corticosteroids, *CUTIVATE* cream is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis under the supervision of a specialist. Expert opinion should be sought prior to the use of *CUTIVATE* cream in other corticosteroid-responsive dermatoses in children.

4.2 Posology and method of administration

Dosage and Administration

Adults, elderly, children and infants aged 3 months and over

Creams are especially appropriate for moist or weeping surfaces.

TREATMENT OF INFLAMMATORY DERMATOSES

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

Atopic dermatitis

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 steroids especially with potent preparations.

Children over 3 months

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

Duration of treatment for children and Infants

When *Cutivate* is used in the treatment of children, if there is no improvement within 7 14 days, treatment should be withdrawn and the child re-evaluated. Once the condition has been controlled (usually within 7-14 days), frequency of application should be reduced to the lowest effective dose for the shortest possible time. Continuous daily treatment for longer than 4 weeks is not recommended

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 Contraindications

The following conditions should not be treated with *CUTIVATE* Cream:

- Untreated cutaneous infections
- Rosacea.
- Acne vulgaris.
- Perioral dermatitis.
- Perianal and genital pruritus
- Pruritus without inflammation
- Dermatoses in infants under 3 months of age, including dermatitis and nappy rash.

4.4 Warnings and Precautions

CUTIVATE Cream 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 a 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.

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.

Use in psoriasis

Topical steroids 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. If used in psoriasis, careful patient supervision is important.

Application to the face

Prolonged application to the face is undersirable 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 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.

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.

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.

Overt suppression of the HPA-axis (morning plasma cortisol less than 5 micrograms/dL) is very unlikely to result from therapeutic use of *CUTIVATE* Cream unless treating more than 50% of an adult's body surface and applying more than 20 g per day.

CUTIVATE Cream 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.

CUTIVATE Cream contains the excipient imidurea which releases traces of formaldehyde as a breakdown product.

Formaldehyde may cause allergic sensitisation or irritation upon contact with the skin.

4.5 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.

4.6 Pregnancy and Lactation

Fertility

There are no data in humans to evaluate the effect of topical corticosteroids on fertility (see Pre-Clinical Safety Data).

Pregnancy

There are limited data from the use of fluticasone propionate 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; however, administration of *CUTIVATE* Cream during pregnancy should only be considered if the expected benefit to the mother is greater than any possible 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.

When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration, there was evidence of fluticasone propionate in the milk.

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

If used during lactation, *CUTIVATE* Cream 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 *CUTIVATE* 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 *CUTIVATE* Cream.

4.8 Undesirable effects

4.8.1: Adverse Reactions

Post-Marketing Data

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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), including isolated reports.

Infections and infestations

Very rare: Opportunistic infection

Immune system disorders

Very rare: Hypersensitivity.

Endocrine disorders

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

Increased weight/obesity

Delayed weight gain/growth retardation in children

Cushingoid features (e.g. moon face, central obesity)

Decreased endogenous cortisol levels

Hyperglycaemia/glucosuria

Hypertension

Osteoporosis

Cataract

Glaucoma

Skin and subcutaneous tissue disorders

Common: Pruritus

Uncommon: Local skin burning

Very rare: Skin thinning, Atrophy, striae, telangiectasias, pigmentation changes, hypertrichosis, allergic contact dermatitis, exacerbation of underlying symptoms, pustular psoriasis, erythema, rash, urticaria.

To report any side effect(s):

Kingdom of Saudi Arabia

-National Pharmacovigilance Centre (NPC)

- Fax: +966-11-205-7662
- Reporting Hotline: 19999
- E-mail: **npc.drug@sfda.gov.sa**
- Website: **https://ade.sfda.gov.sa**

-GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: **saudi.safety@gsk.com**
- Website: **https://gskpro.com/en-sa/**
- P.O Box 55850, Jeddah 21544, Saudi Arabia.

For any information about this medicinal product, please contact:

-GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: **gcc.medinfo@gsk.com**
- Website: **https://gskpro.com/en-sa/**
- P.O. Box 55850, Jeddah 21544, Saudi Arabia

4.9 Overdose

Symptoms and Signs

Topically applied fluticasone propionate 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 appear (see Adverse Reactions).

Treatment

In the event of overdose, *CUTIVATE* Cream 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

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

ATC Code

D07AC Corticosteroid, potent (Group III).

Mechanism of Action

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

Fluticasone propionate is a glucocorticoid with high topical anti-inflammatory potency but low HPA-axis suppressive activity after dermal administration. It therefore has a therapeutic index which is greater than most of the commonly available steroids.
It shows high systemic glucocorticoid potency after subcutaneous administration but very weak oral activity, probably due to metabolic inactivation. In vitro studies show a strong affinity for, and agonist activity at, human glucocorticoid receptors.

Pharmacodynamic Effects

Fluticasone propionate has no unexpected hormonal effects, and no overt, marked effects upon the central and peripheral nervous systems, the gastrointestinal system, or the cardiovascular or respiratory systems.

5.2 Pharmacokinetics Properties

Absorption

Bioavailability is very low after topical or oral administration, due to limited absorption through the skin or from the gastrointestinal tract, and because of extensive first pass metabolism.

Oral bioavailability approaches zero, due to poor absorption and extensive first pass metabolism. Therefore, systemic exposure of fluticasone propionate from any ingestion of *CUTIVATE* Cream will be low.

Distribution

Distribution studies have shown that only minute traces of orally administered compound reach the systemic circulation, and that any systemically available fluticasone propionate is rapidly eliminated in the bile and excreted in the faeces.

Fluticasone propionate does not persist in any tissue and does not bind to melanin.

Metabolism

Pharmacokinetic data for the rat and dog indicate rapid elimination and extensive metabolic clearance. In man too, metabolic clearance is extensive, and elimination is consequently rapid. Thus, drug entering the systemic circulation via the skin will be rapidly inactivated. The major route of metabolism is hydrolysis to a carboxylic acid, which has very weak glucocorticoid or anti-inflammatory activity.

Elimination

In all test animal species the route of excretion was independent of the route of administration of fluticasone propionate. Excretion is predominantly faecal and is essentially complete within 48 hours.

5.3 Pre-clinical Safety Data

Carcinogenesis/Mutagenesis

Carcinogenesis

Long-term topical and oral studies in animals to investigate the carcinogenic potential of fluticasone propionate did not show any evidence of carcinogenicity.

Genotoxicity

Fluticasone propionate was not shown to be mutagenic in a range of in vitro bacterial and mammalian cell assays.

Fertility

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 micrograms/kg per day and to males up to 100 micrograms/kg per day (later reduced to 50 micrograms/kg per day) had no effect upon mating performance or fertility.

Pregnancy

Subcutaneous administration of fluticasone propionate to mice (150 micrograms/kg/day), rats (100 micrograms/kg/day) or rabbits (300 micrograms/kg/day) during pregnancy produced foetal abnormalities including cleft palate. Oral administration did not produce foetal abnormalities, consistent with the low bioavailability of fluticasone propionate by the oral route.

6. Pharmaceutical Particulars

6.1 List of Excipients

Liquid paraffin
Cetostearyl alcohol
Isopropyl myristate
Cetomacrogol 1000
Propylene glycol
Imidurea
Sodium phosphate
Citric acid monohydrate
Purified water.

For important information about some of these excipients see Warnings & Precautions.

6.2 Incompatibilities

No incompatibilities have been identified.

6.3 Shelf-Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

Store below 30°C.

Do not freeze.

The Cream should be used within 60 days from the tube opening.

6.5 Further Information

Instructions for Use/Handling

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

Not all presentations are available in every country.

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