

CUTIVATE

Fluticasone-propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

CLINICAL INFORMATION

Indications

TREATMENT OF INFLAMMATORY DERMATOSES

CUTIVATE Cream is indicated for adults and children for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses such as:

- Eczema including atopic, infantile, and discoid eczemas
- Prurigo nodularis
- Psoriasis (excluding widespread plaque psoriasis)
- Neurodermatoses including lichen simplex
- Lichen planus
- Seborrhoeic dermatitis
- Contact sensitivity reactions
- Discoid lupus erythematosus
- An adjunct to systemic steroid therapy in generalised erythroderma
- Insect bite reactions
- Prickly heat

Dosage and Administration

Pharmaceutical form: Cream

For eczema/dermatitis, apply a thin film of *CUTIVATE* Cream to the affected skin areas once daily.

For all other indications, apply a thin film of *CUTIVATE* Cream to the affected skin areas twice daily.

Calculation of the appropriate dosage for children should allow for their greater surface area to body weight ratio.

Contraindications

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

- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Primary cutaneous viral infections (e.g. herpes simplex, chickenpox)
- Hypersensitivity to any of the ingredients
- Perianal and genital pruritus
- Pruritus without inflammation
- The use of *CUTIVATE* Cream is not indicated in the treatment of primary infected skin lesions caused by infection with fungi or bacteria.
- Dermatoses in children under one year of age, including dermatitis and napkin rash.

Warnings and Precautions

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

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
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- 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

Long-term continuous topical therapy should be avoided where possible, particularly in infants and children, as adrenal suppression can occur even without occlusion.

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 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 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.

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.

Pregnancy and Lactation

Fertility

There are no data in humans to evaluate the effect of topical corticosteroids on fertility (see *Non-Clinical Information*).

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 *Non-Clinical Information*). 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.

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.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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

If signs of hypersensitivity appear, application should stop immediately.

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
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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.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

D07AC17

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.

Pharmacokinetics

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 *CUTIVATE* Cream from any ingestion of fluticasone propionate 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.

Non-Clinical Information

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 studies in the mouse and rat of fluticasone propionate at doses of 150 and 100 micrograms/kg/day respectively, revealed maternal and foetal toxicity characteristic of potent glucocorticoid compounds, including reduction in maternal weight gain, embryonic growth retardation, increased incidences of retarded cranial ossification, and of omphalocele and cleft palate in rats and mice, respectively. In the rabbit, subcutaneous doses of 30 micrograms/kg/day and above were incompatible with sustained pregnancy. This is not unexpected since rabbits are known to be particularly sensitive to glucocorticoid treatment. Following oral administration of fluticasone propionate up to 300 micrograms/kg to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal foetal defects. A very small fraction (<0.005%) of the dose crossed the placenta following oral administration to rats (100 micrograms/kg/day) and rabbits (300 micrograms/kg/day).

PHARMACEUTICAL INFORMATION

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.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.
Do not freeze.

Nature and Contents of Container

As registered locally.

Incompatibilities

No incompatibilities have been identified.

Use and 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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