# Cutivate

**Version GDSv15/IPIv05**

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## Fluticasone propionate

## Qualitative and Quantitative Composition

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

## Clinic Information

## Directions

### Treatment of Inflammatory Dermatoses

***CUTIVATE*** Cream is a potent topical corticosteroid indicated in adults, children and infants 3 months of age or older for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

These include:

- Atopic dermatitis (including childhood atopic dermatitis)
- Nummular dermatitis (discoid eczema)
- Nodular prurigo
- Psoriasis (excluding disseminated plaque psoriasis)
- Lichen simplex chronicus (neurodermatitis) and lichen planus
- Seborrheic dermatitis
- Irritant or allergic contact dermatitis.
- Discoid lupus erythematosus
- As an adjunct to systemic corticosteroid therapy in generalized erythroderma
- Reactions to insect bites
- Miliaria (miliary fever)

### Reduced Risk of Relapse

***CUTIVATE*** Cream is indicated for decreasing the risk of relapse in patients with recurrent chronic atopic dermatitis once an acute episode has been effectively treated.

## Dosage and Administration

### Pharmaceutical Form

Cream

### Adults, Elderly, Children and Infants 3 Months and Older

The creams are especially suitable for wet or oozing surfaces.

#### Treatment of Inflammatory Dermatoses

Apply a thin film and rub in gently, using just enough to cover the entire affected area, once or twice a day for no more than 4 weeks, until there is improvement, and then reduce the frequency of application or switch 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 reevaluated.

#### Atopic dermatitis

Topical corticosteroid therapy should be tapered off gradually after control is achieved and an emollient should be continued as supportive therapy.

Recurrence of pre-existing dermatoses may occur with sudden discontinuation of topical corticosteroids, especially with potent preparations.

#### Reduced Risk of Relapse

Once an acute episode has been effectively treated, the frequency of application should be reduced to one application daily, twice a week, without occlusion. Application should be continued in all previously affected areas or in areas that are sites of possible relapse. This regimen should be combined with routine daily use of emollients. The condition should be reevaluated regularly.

### Children Over 3 Months

In children, local and systemic side effects of topical corticosteroids are more likely and generally require shorter courses and less potent agents than adults.

When using ***CUTIVATE*** Cream, care should be taken to ensure that the amount applied is the minimum that provides therapeutic benefit.

### Elderly

In clinical studies, no differences in responses have been identified between elderly and younger patients. The increased frequency of decreased liver or kidney function in the elderly may slow elimination if systemic absorption occurs. Therefore, the minimum amount should be used for the shortest possible time to achieve the desired clinical benefit.

### Renal/hepatic dysfunction

In case of systemic absorption (when the application is over a large surface area for a prolonged period), metabolism and elimination may be delayed, thus increasing the risk of systemic toxic effects. Therefore, the minimum amount should be used for the shortest possible time to achieve the desired clinical benefit.

## Contraindications

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

- Untreated skin infections
- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Perianal and genital pruritus
- Itching without inflammation
- Dermatoses in infants younger than 3 months of age, including dermatitis in general and diaper rash.

## Warnings and Precautions

***CUTIVATE*** Cream should be used with caution in patients with a history of local hypersensitivity to corticosteroids or any of the excipients in the preparation. Local hypersensitivity reactions (*see ADVERSE REACTIONS*) may resemble symptoms of the condition being treated.

In some individuals, hypercortisolism (Cushing's syndrome) and reversible inhibition of the hypothalamic-pituitary-adrenal (HHS) axis, resulting in glucocorticoid insufficiency, may occur as a result of increased systemic absorption of topical corticosteroids. If any of these manifestations are observed, gradually withdraw the drug by reducing the frequency of its application or replacing it with another less potent corticosteroid. Sudden discontinuation of treatment may result in glucocorticoid insufficiency (*see ADVERSE REACTIONS*).

Risk factors for increased systemic effects are:

- Potency and formulation of topical corticosteroid
- Duration of exposure
- Application over a large surface area
- Use on occluded areas of skin, e.g. in intertriginous areas or under occlusive dressings (in infants the diaper may act as an occlusive dressing)
- Increased hydration of the stratum corneum
- Use on thin skin areas, such as the face
- Use on denuded skin or other conditions where there is impaired skin barrier function
- Compared to adults, children and infants may absorb proportionately larger amounts of topical corticosteroids and therefore be more susceptible to systemic adverse effects. This is because children have immaturity of skin barrier function and ratio of surface area to body weight greater than adults.

Visual disturbance has been reported in patients using systemic and/or topical corticosteroids. If a patient has blurred vision or other visual disturbances, consider evaluating possible causes which may include cataracts, glaucoma, or central serous chorioretinopathy.

### Children

In infants and children younger than 12 years of age, continuous long-term topical corticosteroid treatment should be avoided whenever possible, as adrenal suppression is more likely to occur.

### Use in Psoriasis

Topical steroids should be used with caution in patients with psoriasis, as recurrence, tolerance development, risk of generalized pustular psoriasis, and development of local or systemic toxicity have been reported in some cases due to impaired barrier skin function. If used in psoriasis, it is important to carefully monitor the patient.

### Application on the Face

Prolonged application on the face is inadvisable, as this area is more susceptible to atrophic changes.

### Application on the Eyelids

If applied to the eyelids, it is necessary to take care to prevent the preparation from entering the eyes, as repeated exposure could lead to cataracts and glaucoma.

### Concomitant infection

Appropriate antimicrobial treatment should be used whenever inflammatory lesions that have become infected are treated. If the infection spreads, it is necessary to discontinue treatment with topical corticosteroid and administer appropriate antimicrobial therapy.

### Risk of Infection with Occlusion

Bacterial infections are facilitated by hot and humid conditions in skin folds or due to occlusive dressings. When occlusive dressings are used, the skin should be cleaned before applying a new dressing.

### Chronic Leg Ulcers

Topical corticosteroids are sometimes used to treat dermatitis around chronic leg ulcers. However, such use could be associated with an increase in the occurrence of local hypersensitivity reactions and increased risk of local infection.

Frank suppression of the HHS axis (morning plasma cortisol value less than 5 micrograms/dL) is very unlikely to occur with therapeutic use of ***CUTIVATE*** Cream, unless more than 50% of an adult's body surface area is treated and more than 20 g per day is applied.

***CUTIVATE*** cream contains paraffin. Instruct patients not to smoke or go near exposed flames because of the risk of severe burns. Fabrics (clothing, bedding, bandages, etc.) that have been in contact with this product burn more easily and pose a serious fire hazard. Washing clothes and bedding can reduce product buildup, but not completely remove it.

***CUTIVATE*** Cream contains imidurea as an excipient, which releases minute amounts of formaldehyde as a product of its decomposition. Formaldehyde can cause allergic sensitization or irritation on contact with skin.

## Interactions

Concomitantly administered drugs that may inhibit CYP3A4 (e.g., ritonavir or itraconazole) have been shown to inhibit corticosteroid metabolism and lead to increased systemic corticosteroid exposure. The extent to which this interaction is clinically important depends on the dose and route of administration of corticosteroids and the potency of the CYP3A4 inhibitor.

## Pregnancy and Lactation

### Fertility

There are no human data to assess the effect of topical corticosteroids on fertility *(see Preclinical Information a).*

### Pregnancy

There are limited data from the use of fluticasone propionate in pregnant women.

Topical administration of corticosteroids to pregnant females may cause abnormalities in fetal development (*see Preclinical Information a).* The importance of this data in humans has not been established; but administration of ***CUTIVATE*** Cream during pregnancy should only be considered if the intended benefit to the mother outweighs the possible risk to the foetus. The minimum amount should be used for the shortest possible time.

### Nursing

The safe use of topical corticosteroids during breastfeeding has not been established.

It is unknown whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in human milk.

When measurable plasma levels were obtained in lactating laboratory rats after subcutaneous administration, there was evidence of fluticasone propionate in 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 while breastfeeding, ***CUTIVATE*** Cream should not be applied to the breast area, to prevent accidental ingestion by the infant.

## Effects on the Ability to Drive Vehicles and the Use of Machinery

No studies have been conducted to investigate the effect of ***CUTIVATE*** on driving performance or the ability to operate machinery. No detrimental effect is anticipated to occur in such activities, from the adverse reaction profile of topical application of ***CUTIVATE*** Cream.

## Adverse Reactions

### Post-Market Data

Adverse drug reactions (ADRs) are listed below according to the MedDRA dictionary class of organ systems and their frequency. Their frequency is defined as very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), uncommon (≥1/10000 and <1/1000) and very uncommon (<1/10000), including isolated reports.

#### Infections and Infestations

Very rareOpportunistic infections

#### Immune System Disorders

Very rareHypersensitivity

#### Endocrine Disorders

Very rareHypothalamic-pituitary-adrenal (HHS) axis suppression: Weight gain/obesity, Delayed weight/growth in children, Cushingoid traits (e.g., moon face, central obesity), Decreased endogenous cortisol levels, Hyperglycemia/glycosuria, Hypertension, Osteoporosis, Cataracts, Glaucoma

#### Skin and Subcutaneous Tissue Disorders

Common pruritus
Uncommon Localized burning skin
Very uncommonThinning of the skin, atrophy, stretch marks, telangiectasias, pigmentation changes, hypertrichosis, allergic contact dermatitis, exacerbation of underlying symptoms, pustular psoriasis, erythema, rash, urticaria.

## Overdose

### Symptoms and Signs

Fluticasone propionate applied topically may be absorbed in sufficient amounts to produce systemic effects.

Although acute overdose is very unlikely, features of hypercortisolism may occur in the case of chronic overdose or abuse (*see ADVERSE REACTIONS*).

### Treatment

In case of overdose, ***CUTIVATE*** Cream should be withdrawn gradually by reducing the frequency of its application or replacing it with a less potent corticosteroid, due to the risk of glucocorticoid insufficiency.

Further management should be as clinically indicated or recommended by the national poison center in countries where it exists.

# Pharmacological properties

## Pharmacodynamics

### ATC Code

D07AC (Potent corticosteroid [Group III]).

### Mechanism of action

Topical corticosteroids possess anti-inflammatory, antipruritic and vasoconstrictive properties. They act as anti-inflammatory agents through multiple mechanisms to inhibit late-phase allergic reactions, including decreasing mast cell density, decreasing chemotaxy and eosinophil activation, decreasing cytokine production in lymphocytes, monocytes, mast cells, and eosinophils, and inhibiting arachidonic acid metabolism.

Fluticasone propionate is a topical glucocorticoid of high anti-inflammatory potency and with low suppressive activity of the HHS axis after dermal administration. Therefore, it has a higher therapeutic index than many commonly available corticosteroids.

It has high systemic glucocorticoid potency after subcutaneous administration; but very weak oral activity, probably due to metabolic inactivation. *In in vitro studies*, a strong affinity with human glucocorticoid receptors and their agonist activity in them is shown.

### Pharmacodynamic effects

Fluticasone propionate has no unexpected hormonal effects or significant frank effects on the central and peripheral nervous system, gastrointestinal system, cardiovascular system or respiratory system.

## Pharmacokinetics

### Absorption

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

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

### Distribution

In distribution studies, it has been shown that only minute amounts of the orally administered compound reach the general circulation and that systemically available fluticasone propionate is rapidly eliminated in the bile and excreted in the feces.

Fluticasone propionate does not persist in any tissue or bind with melanin.

### Metabolism

Pharmacokinetic data in rats and dogs indicate rapid elimination and extensive metabolic clearance. In man, metabolic clearance is also extensive and, consequently, elimination is rapid. Thus, the drug that enters the general circulation through the skin is quickly inactivated. The main route of metabolism is hydrolysis to a carboxylic acid, which possesses 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.

## Preclinical Information

### Carcinogenesis/Mutagenesis

#### Carcinogenesis

Long-term topical and oral animal studies to investigate the carcinogenic potential of fluticasone propionate showed no evidence of carcinogenicity.

#### Genotoxicity

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

#### Fertility

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

#### Pregnancy

Subcutaneous administration of fluticasone propionate to female mice (150 micrograms/kg/day), female rats (100 micrograms/kg/day) or rabbits (300 micrograms/kg/day) during pregnancy resulted in abnormalities of fetal development, including cleft palate. Oral administration did not produce abnormalities of fetal development, which is consistent with the low bioavailability of oral fluticasone propionate.

# Pharmaceutical Information

## List of Excipients

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

For important information about some of these excipients, see Warnings and precautions.

## Life

The expiration date is indicated on the packaging.

## Special Storage Precautions

Store at less than 30 C.

Do not freeze.

## Nature and contents of the pack

As locally registered.

Not all presentations are available in all countries.

## Incompatibilities

No incompatibilities have been identified.

# Use and Management

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

Not all presentations are available in all countries.

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