PRODUCT MONOGRAPH

[Pr]Cutivate®

Fluticasone propionate

Cream, 0.05%

Topical Anti-inflammatory Corticosteroid

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Fluticasone Priopionate Cream, 0.05% w/w	Imidurea, as a preservative *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CUTIVATE® (fluticasone propionate) Cream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Studies performed with CUTIVATE® indicate that it is in the medium range of potency as compared with other topical corticosteroids.

Pediatrics (< 12 years of age): CUTIVATE® is not indicated in children under the age of 12 years old.

CONTRAINDICATIONS

- CUTIVATE® is not indicated in patients with a hypersensitivity to this drug or to any of the ingredients in the formulation (for a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING) or to other corticosteroids.

- It is also contraindicated in patients with viral (e.g., herpes or varicella) lesions of the skin, bacterial or fungal skin infections, parasitic infections, skin manifestations relating to tuberculosis or syphilis, eruptions following vaccinations , rosacea, acne vulgaris, perioral dermatitis, perianal and genital pruritus, pruritus without inflammation and dermatoses in children, including dermatitis and diaper rash.

- CUTIVATE® is not indicated for topical application to the eye.

WARNINGS AND PRECAUTIONS

General

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

CUTIVATE® should not be used under occlusive dressing, due to increased risk of systemic exposure and infection. When used under occlusive dressing, over extensive areas or on the face, scalp, axillae or scrotum, sufficient absorption may occur to result in adrenal suppression and other systemic effects (see WARNINGS AND PRECAUTIONS – Endocrine and Metabolism, Immune and Ophthalmologic).

Cardiovascular

Suitable precautions should be taken when using topical corticosteroids in patients with stasis dermatitis and other skin diseases with impaired circulation.

Use of corticosteroids around chronic leg ulcers may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Endocrine and Metabolism

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption while on therapy.

If patients must be treated over large body surface areas, they should be evaluated periodically for evidence of HPA axis suppression (see WARNINGS AND

PRECAUTIONS – Monitoring and Laboratory Tests). Other conditions which augment systemic absorption include the application of topical corticosteroids to intertriginous areas (such as the axillae), or prolonged use. Other risk factors for increased systemic effects include increasing hydration of the stratum corneum, use on thin skin areas (such as the face), use on broken skin or conditions where the skin barrier may be impaired, application to a large area of skin and the formulation and potency of the topical corticosteroid.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface to body mass ratios (see WARNINGS AND PRECAUTIONS – Special Populations, Pediatrics).

Topical steroids should be used with caution in psoriasis as rebound relapses, development of tolerance, risk of generalized 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.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug by reducing the frequency of application or to substitute a less potent drug. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical glucocorticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur that require supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Immune

Topical corticosteroids may increase the risk of infections including aggravation of cutaneous infection, masked infection and secondary infections. In particular, bacterial infection is encouraged by the warm, moist conditions within skin folds. If concomitant skin infections develop, CUTIVATE® should be discontinued and antimicrobial therapy administered.

Ophthalmologic

Topical corticosteroids should be used with caution on lesions close to the eye because systemic absorption may cause increased intraocular pressure, glaucoma or cataracts.

Sensitivity

Local hypersensitivity reactions (see ADVERSE REACTIONS) may resemble symptoms of the condition under treatment. If hypersensitivity reactions occur, the drug should be discontinued and appropriate therapy initiated.

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

Skin

CUTIVATE® contains the excipient imidurea which releases traces of formaldehyde as a breakdown product. Formaldehyde may cause allergic sensitization or irritation upon contact with the skin.

If irritation develops, CUTIVATE® should be discontinued and appropriate therapy instituted.

Prolonged use of topical corticosteroid preparations may produce striae or atrophy of the skin or subcutaneous tissue. Topical corticosteroids should be used with caution on lesions of the face, groin and axillae as these areas are more prone to atrophic changes than other areas of the body. Frequent observation is important if these areas are to be treated. If skin atrophy is observed, treatment should be discontinued.

Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerances, risk of generalized 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.

Special Populations

Pregnant Women: There are limited data from the use of fluticasone propionate in pregnant women. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dose levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. The relevance of this animal finding to humans has not been established. CUTIVATE® should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus. The minimum quantity should be used for the minimum duration.

Nursing Women: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration, there was evidence of fluticasone propionate in the milk. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when CUTIVATE® is administered to a nursing woman. Administration of CUTIVATE® during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant. If used during lactation, CUTIVATE® should not be applied to the breasts to avoid accidental ingestion by the infant.

Pediatrics (< 18 years of age): Safety and effectiveness in children and infants have not been established. Because of a higher ratio of skin surface to body mass, children are at greater risk than adults of HPA axis suppression when they are treated with topical

corticosteroids. Therefore, they are also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. Calculation of the appropriate dosage for children should allow for their greater surface area to body weight.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headache, and bilateral papilledema. Chronic corticosteroid therapy may interfere with the growth and development of children.

Long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression is more likely to occur. Care should be taken when using CUTIVATE® to ensure the amount applied is the minimum that provides the therapeutic benefit.

Geriatrics (> 65 years of age): In general, topical corticosteroids should be used cautiously in elderly patients, reflecting their increased skin fragility and greater frequency of hepatic, renal or cardiac dysfunction, and of concomitant disease or other drug therapy. 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.

Patients with renal / hepatic impairment: In case of systemic absorption , 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.

Monitoring and Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression: ACTH stimulation test; A.M. plasma cortisol test; urinary free cortisol test.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In controlled clinical trials, the total incidence of adverse reactions associated with the use of CUTIVATE® was approximately 4%. These adverse reactions were mild and self-limiting and consisted primarily of pruritus, dryness, numbness of fingers, and burning. These events occurred in 2.9%, 1.2%, 1.0% and 0.6% of patients, respectively.

The following additional local adverse reactions have been reported infrequently with other topical corticosteroids, and they may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, dilation of the superficial blood vessels and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical steroid products.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In a clinical study that compared once daily to twice daily dosing of CUTIVATE®, the local adverse events (≥ 1%) that were considered to be drug related are summarized in Table 1. In addition, the less common drug-related adverse events (< 1%) from this study are presented following Table 1.

Table 1 Drug-related adverse events (≥ 1%) in clinical study comparing once daily to twice daily dosing of CUTIVATE®

System Organ Class (Preferred Term)	CUTIVATE® once daily n= 125	CUTIVATE® twice daily n= 125
Skin and subcutaneous tissue disorders		
Infected eczema	1 (0.8%)	2 (1.6%)
Exacerbation of eczema	4 (3.0%)	1 (0.8%)
Erythema	0	2 (1.6%)
Burning	0	2 (1.6%)
Skin irritation	6 (4.5%)	1 (0.8%)
Pruritus	2 (1.5%)	3 (2.3%)
Exacerbation of pruritis	4 (3.0%)	1 (0.8%)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Skin and subcutaneous tissue disorders: skin infection, viral warts, herpes simplex, impetigo, atopic dermatitis, eczema, stinging, folliculitis, blisters, dryness of skin

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of the drug. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity, opportunistic infection

Endocrine disorders: hypothalamic-pituitary adrenal (HPA) axis suppression, including increased weight / obesity, delayed weight gain/growth retardation in children, Cushingoid features (e.g. moon face, central obesity), decreased endogenous cortisol levels, hyperglycemia / glucosuria, hypertension, osteoporosis,

Eye disorders: cataract, glaucoma

Skin and subcutaneous tissue disorders: pruritus, local skin burning, skin thinning, atrophy, striae, telangiectasias, pigmentation changes hypertrichosis, allergic contact dermatitis, exacerbation of underlying symptoms, pustular psoriasis, erythema, rash, urticaria

DRUG INTERACTIONS

Overview

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.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients should be instructed to use CUTIVATE® for the minimum amount of time necessary to achieve the desired results because of the potential for corticosteroids to suppress the hypothalamic-pituitary-adrenal (HPA) axis and cause skin atropy (see WARNINGS AND PRECAUTIONS).

- CUTIVATE® is for topical use only and not for ophthalmic use.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface to body weight ratios.

CUTIVATE® should be used with caution in patients > 65 years of age who may be more susceptible to percutaneous absorption and the potential effects of systemic absorption. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs.

Recommended Dose and Dosage Adjustment

Eczema: Apply a thin film of CUTIVATE® to the affected skin areas once or twice daily. Rub in gently.

Other Corticosteroid Responsive Dermatoses: Apply a thin film of CUTIVATE® to the affected skin areas twice daily. Rub in gently.

Avoid abrupt discontinuation of topical corticosteroids when control is achieved as rebound of pre-existing dermatoses can occur.

If the skin condition does not improve within two to four weeks, treatment and diagnosis should be re-evaluated.

Pediatrics: CUTIVATE® is not indicated for use in children under 12 years of age.

Geriatrics (>65 years of age): CUTIVATE® should be used with caution due to increased risk of renal or hepatic impairment in this population.

Renal/Hepatic Impairment: The minimum quantity should be used for the shortest duration to achieve the desired clinical benefit (see WARNINGS AND PRECAUTIONS — Special Populations, Patients with renal / hepatic impairment).

Missed Dose

Any missed dose should be applied as soon as possible and then continue with the regular frequency of doses (i.e., no extra doses should be applied).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Topically applied CUTIVATE® can be absorbed in sufficient amounts to produce systemic effects (see WARNINGS AND PRECAUTIONS).

In case of chronic overdosage or misuse, the features of hypercorticism may appear. As with any corticosteroid, treatment should be discontinued if the symptoms of hypercorticism appear. It is important that the treatment is gradually withdrawn 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fluticasone propionate is a synthetic, fluorinated corticosteroid. Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, anti-pruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid, which is released from membrane phospholipids by phospholipase A2.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin, while inflammation and/or other disease processes in the skin increase percutaneous absorption.

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity to the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors. The therapeutic potency of

glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. Fluticasone propionate binding to the glucocorticoid receptor is rapid.

The half life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

In human volunteers, fluticasone propionate was 9.5 times more potent than fluocinolone acetonide and intermediate in potency between betamethasone-17-valerate (less potent) and clobetasol-17-propionate (more potent).

Fluticasone propionate absorbed systemically is rapidly metabolized in the liver by esterase-catalyzed hydrolysis to the 17-beta-carboxylic acid which has no significant glucocorticoid or anti-inflammatory activity.

Human Pharmacokinetics

Absorption: The pharmacokinetic characteristics following administration of fluticasone propionate in man are similar to those of other glucocorticoids, except that oral bioavailability is extremely low. This low oral bioavailability, coupled with high plasma clearance and efficient biliary excretion of metabolites, enhances the topical versus systemic effects.

Distribution: Single intravenous doses of 2 mg in healthy volunteers revealed that the clearance of fluticasone propionate approximates liver blood flow, with renal clearance accounting for less than 1%. These results indicate that hepatic extraction is almost complete and that oral bioavailability is close to zero. The plasma elimination half-life is approximately 3 hours, and the volume of distribution is approximately 260 L.

Metabolism: Pharmacokinetic data from man indicate that clearance is high relative to hepatic blood flow. Consequently, first-pass metabolism is extensive and oral bioavailability is negligible.

Excretion: Studies with radio labelled and unlabelled fluticasone propionate administered orally to human volunteers indicate that the majority of the dose (87%-100%) is excreted in the feces, with up to 75% as unchanged drug, depending on the dose administered. Between 1% and 5% of the dose is excreted as metabolites in urine.

Occlusion

The poor penetration of fluticasone propionate, suggested from the minimal effects on the HPA axis, was also evidenced by low plasma concentrations after dermal application. The application of 12.5 g of 0.05% fluticasone propionate cream twice daily for 21 days without occlusion to healthy male volunteers resulted in trough plasma concentrations generally below the limit of detection (0.05 ng/mL) throughout the study.

Maximum trough levels of 0.069 to 0.39 ng fluticasone propionate/mL were observed following the twice daily application of 50 g of 0.05% fluticasone propionate cream under occlusion for 5 days.

HPA axis suppression

No evidence of HPA axis suppression was seen in 45 healthy volunteers who repeatedly applied large amounts (between 30 g and 50 g per day) of fluticasone propionate cream formulations with or without occlusion. This was despite the fact that 15 of the 45 volunteers had applied 0.05% fluticasone propionate ointment (a ten-fold higher concentration of ointment than that marketed). The minimal effects on the HPA axis probably result from the relatively poor penetration of fluticasone propionate through the various layers of the skin.

Fluticasone propionate cream, 0.05% produced HPA axis suppression within seven days when used at a dose of 30 g per day in diseased patients. In a study of the effects of Fluticasone propionate cream, 0.05% on the HPA axis, a total of 30 g per day was used in two applications daily for seven days to six patients with psoriasis or atopic dermatitis involving at least 30% of the body surface. One patient developed evidence of adrenal suppression after six days of treatment with a below normal plasma cortisol level that returned to low normal levels the following day. Another patient developed a 60% decrease (although never below normal) in the plasma cortisol level from pre-treatment values after 2 days of treatment. This suppression persisted at this level for 48 hours before recovering by day six of treatment. The results of this study indicate that Fluticasone propionate cream, 0.05% may be able to suppress the HPA axis within a few days with a dose of 30 g per day.

Sensitivity studies

Specialized studies have shown fluticasone propionate to have no potential to cause irritancy, contact sensitization, photo toxicity or photo contact allergenicity, despite the aggressive nature of the dosing schedules employed. Fluticasone propionate ointment (0.05%) and cream (0.005% and 0.05%) preparations were applied in volumes of 0.1 mL for up to 26 days in these specialised studies.

STORAGE AND STABILITY

Store between 2° and 30°C. Do not freeze. Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Available in 15, 30 and 60 g tubes.

Each gram of CUTIVATE® contains fluticasone propionate 500 micrograms in a cream base.

Non-medicinal ingredients: propylene glycol, mineral oil, cetostearyl alcohol, polyoxyl 20 cetostearyl ether, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water and imidurea as a preservative.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

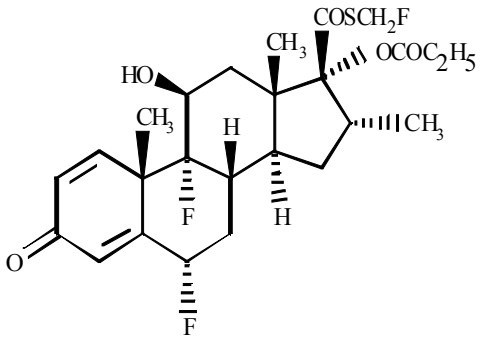
Proper name: Fluticasone proprionate (BAN, INN, USAN)

Chemical name: S-fluoromethyl 6α,9α-difluoro-llβ-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-l,4-diene-17β-carbothioate

Molecular formula: $C_{25}H_{31}F_30_5S$

Molecular mass: 500.6

Structural formula:



Physicochemical properties: A white to off-white powder

Solubility:

- Freely soluble in dimethyl sulfoxide and dimethylformamide.
- Sparingly soluble in acetone, dichloromethane, ethyl acetate and chloroform.
- Slightly soluble in methanol and 95% ethanol.
- Practically insoluble in water.

Melting point: Decomposes without melting, onset of decomposition occurs at about 225°C.

DETAILED PHARMACOLOGY

Animal

Fluticasone propionate was shown to be approximately twice as potent in topical activity as beclomethasone according to the McKenzie vasoconstrictor assay.

Although relative vasoconstrictor activity does not necessarily imply similar relative therapeutic efficacy, evidence for local anti-inflammatory action without systemic effects has been demonstrated by studies in laboratory animals and confirmed in human clinical pharmacology studies.

Animal studies of the relative anti-inflammatory and hypothalamic-pituitary-adrenal (HPA) axis inhibitory potencies of topically applied drug demonstrated that fluticasone propionate has an advantageous therapeutic index (>200 times that of beclomethasone dipropionate).

Studies in rodents were conducted to quantitate and compare anti-inflammatory activity after topical administration of fluticasone propionate and the ability to produce specific systemic steroid-related effects after topical, oral or parenteral administration.

Topical anti-inflammatory activity was measured in rats and mice using the inflammatory response to croton oil applied topically to the ear. Results showed that fluticasone propionate was essentially equipotent with fluocinolone acetonide in both rats and mice.

Systemic responses to repeated topical applications of fluticasone propionate were assessed by measurement of thymus involution and reduction in stress-induced plasma corticosterone (HPA axis suppression) in rats and mice, and adrenal atrophy in the rat. In these tests, fluticasone propionate was 50-100-fold less potent than fluocinolone acetonide in the rat (56-fold greater therapeutic index) and 100 times less potent than fluocinolone acetonide in mice (relative therapeutic index 91). Therefore, in both species, the separation between topical anti-inflammatory and systemic activity after topical application was highly favourable to fluticasone propionate.

Comparison of systemic activity after topical and subcutaneous dosing of fluticasone propionate showed that, in both rats and particularly in mice, fluticasone propionate is more potent when given subcutaneously.

In rats, fluticasone propionate given subcutaneously was compared with betamethasone alcohol and fluocinolone acetonide using thymus involution, adrenal atrophy, and inhibition of carrageenin granuloma formulation as assessments of systemic activity. Fluticasone propionate was equipotent with betamethasone alcohol and between 13 and 38 times less potent than fluocinolone acetonide.

In mice, using thymus involution and HPA axis suppression, fluticasone propionate given subcutaneously, was approximately equipotent with betamethasone alcohol and approximately 4 times less potent than fluocinolone acetonide.

After oral dosing in the rat, fluticasone propionate caused some thymus involution, adrenal atrophy and HPA axis suppression but was 6 to 38 times less potent than betamethasone alcohol. In the mouse, oral fluticasone propionate is 60 to 200 times less potent than betamethasone alcohol.

Pharmacodynamics:

Fluticasone propionate was screened for a wide range of steroid hormonal or anti-hormonal activity. To ensure significant systemic exposure fluticasone propionate was administered subcutaneously to rats and mice, and was found to be devoid of androgenic, anabolic, oestrogenic, and anti-gonadotrophic activity. Fluticasone propionate had some progestational activity in oestrogen-primed weanling rabbits, and also showed some anti-androgenic and anti-oestrogenic activity. Weak anti-anabolic activity, another characteristic of potent glucocorticoids, was observed in the castrated rat. Fluticasone propionate lacked mineralocorticoid activity but caused significant diuresis and urinary excretion of sodium and potassium.

Pharmacokinetics:

Pharmacokinetic data from rat and dog indicate that clearance is high relative to hepatic blood flow. Consequently, first-pass metabolism is extensive and oral bioavailability is negligible.

Studies examining the distribution of radio labelled fluticasone propionate in the rat have shown that orally-administered drug is absorbed and then excreted in the bile on first-pass through the liver. Thus, only minute traces of radioactivity pass into the systemic circulation.

The vast majority of a radio labelled dose following intravenous (rat and dog), oral and subcutaneous (mouse, rat and dog) administration is excreted via the feces, and evidence from bile duct-cannulated animals indicates that the major route of excretion is via the bile. Renal excretion is of minor importance, as urinary excretion accounts for less than 5% of a parenteral dose. No unchanged drug is excreted in the bile of rats or dogs, but a significant amount, (up to 40%) of unchanged compound was found in the feces of dogs dosed orally with fluticasone propionate.

Thus, the low oral bioavailability of fluticasone propionate expected due to extensive first-pass metabolism is compounded by incomplete absorption from the gastrointestinal tract particularly in the dog. The major route of metabolism in rat, dog and humans is the hydrolysis of the fluorinated carbothioate group to yield the inactive carboxylic acid.

When administered orally to pregnant rats (100 µg/kg) or rabbits (300 µg/kg), a very small fraction of the dose (<0.005%) passes across the placenta.

Studies performed in rats following topical administration of radio labelled fluticasone propionate cream or ointment have shown that only about 5% of the dose is absorbed through the skin, the majority of which is excreted in the feces. The majority of the dose (73%) is recovered from the surface of the application site. Fluticasone propionate is stable and is not metabolized by dermal enzymes when incubated with human skin homogenates in vitro or when applied dermally to rats.

TOXICOLOGY

Acute Toxicity
Pharmacokinetic studies in the rat have shown that only 5% of the dermal dose is absorbed through the skin.

However, intravenous and subcutaneous dosing allows toxicity to be fully characterised after maximal systemic exposure.

The results of the acute toxicity studies with fluticasone propionate administered by inhalation, orally, subcutaneously and intravenously, demonstrated a large margin of safety over the anticipated exposure of humans following the dermal application of ointment or cream preparations containing 0.005% and 0.05% fluticasone propionate, respectively. Systemic exposure following the dermal application of 0.05% cream or 0.005% ointment would be 45 μg/kg or 4.5 μg/kg, respectively, assuming human percutaneous absorption of approximately 5% and the use in a 50 kg person of 90 g of cream or ointment in one day. The approximate LD_{50} values are shown in Table 2.

Table 2 Approximate animal LD_{50} values

Species	Route	Approx. LD_{50} (mg/kg)
Mouse	Oral	>1000
Rat	Oral	>1000
Mouse	Subcutaneous	>1000
Rat	Subcutaneous	>1000
Rat	Intravenous	>2
Rat	Inhalation	>1.66
Dog	Inhalation	>0.82

High oral doses of 1 g/kg were well tolerated in both the mouse and rat. The only (reversible) changes observed were a slowing in growth rate and microscopically-evident cortical depletion of the thymus of animals killed 3 days after dosing.

Subcutaneous doses of fluticasone propionate at 1 g/kg were administered to mice and rats. Animals progressively lost condition and body weight and the effects seen were thymic depletion and various lesions associated with a compromised immune system. In addition, gastric steroid ulcers were seen. These observed changes are the expected response to glucocorticoid therapy. The lack of reversible thymic effects in subcutaneously-dosed animals is almost certainly due to the deposition and leaching of insoluble steroid from the injection site.

When given intravenously to rats at a dose of 2 mg/kg, the only changes seen were slightly subdued behaviour immediately after treatment and reversible thymic involution.

Chronic Toxicity

Subacute toxicity studies were conducted in adult and juvenile rats for periods up to 35 days and in Beagle dogs for periods up to 44 days. Fluticasone propionate was administered in Table 3.

Table 3 Subacute toxicity in rats and Beagle dogs

Species	Route	Doses*	Dosing Period
Rat	Oral (gavage)	1000 μg/kg/day	15 days
Dog	Oral (gavage)	3000 μg/kg/day	7 days
Rat	Subcutaneous	250/90 μg/kg/day	36 days
		10 μg/kg/day	35 days
Dog	Subcutaneous	160 μg/kg/day	36 days
Rat	Inhalation	60 μg/L/day	7 days
		18.2 μg/L/day	14 days
		475 μg/L/day	30 days
Dog	Inhalation	20 mg/animal/day	10 days
		9 mg/animal/day	44 days

Key: * - maximum dose of fluticasone propionate administered.

Clinical observations were similar for all routes of administration in both species. These consisted of reduced weight gain and general loss of condition. Inhalation studies in the dog resulted in clinical signs associated with the administration of a potent glucocorticoid and were consistent with the symptoms of Canine Cushing's Syndrome.

Changes typical of glucocorticoid overdosage were seen in both haematological and clinical chemistry parameters. Effects were seen on the red cell parameters and a characteristic leukopenia resulting from a lymphopenia accompanied by a neutrophilia. Endogenous cortisol and corticosterone were depressed in dogs and rats respectively.

Microscopic pathology was again consistent with the administration of a potent glucocorticoid showing thymic and adrenal atrophy, lymphoid depletion in rats and dogs and glycogenic vacuolation of the liver in dogs.

There were no specific effects on the maturation of juvenile rats after subcutaneous dosing.

The application of a cream formulation containing 0.05% fluticasone propionate and an ointment containing 0.05, 0.10 or 0.20% w/w fluticasone propionate to the abraded skin of rats for up to 35 days did not compromise the healing of damaged areas of skin. Some skin thinning was observed at the site of application. Expected glucocorticoid effects, namely reduced body weight gain and slight changes in hematology and clinical chemistry, were observed. However, absorption of fluticasone propionate was of a low order as no significant differences were observed in the corticosterone levels between treated and control animals.

Fluticasone propionate ointment was well tolerated following daily applications to the skin of the rat at dose levels of 0.05, 0.10 and 0.20% w/w for 26 weeks. Thinning of the skin at the application sites, due to slight to moderate thinning of the dermal collagen, together with loss of fat was observed.

Daily dermal administration of 0.8% w/w of fluticasone propionate ointment under occlusion for up to 6.5 hours per day to Beagle dogs for 26 weeks was also well tolerated. A single papilloma was observed at the treatment site in each of 2 dogs at the high dose level. This may have been a consequence of local immunosuppression. Three dogs at the high dose level showed moderate to large diffuse corneal opacities at the end of treatment. These animals had intercurrent ocular infections during the study. Increased susceptibility to ocular infection in these dogs may have occurred in part as a result of the recognised immunosuppressive effect of corticosteroids.

Mutagenicity

Fluticasone propionate did not induce gene-mutation in prokaryotic microbial cells and there was no evidence of toxicity or gene-mutational activity in eukaryotic Chinese hamster cells in vitro. The compound did not induce point-mutation in the Fluctuation assay, and did not demonstrate gene-convertogenic activity in yeast cells. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro and fluticasone propionate was not demonstrably clastogenic in the mouse micronucleus test when administered at high doses by oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

Reproduction and Teratology
Subcutaneous studies in the mouse and rat at 150 and 100 μg/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 omphalocoele and cleft palate in rats and mice, respectively. In the rabbit, subcutaneous doses of 30 μg/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 μg/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 μg/kg/day) and rabbits (300 μg/kg/day).

Carcinogenicity
No treatment related effects were observed on the type or incidence of neoplasia in an 80 week dermal oncogenicity study in mice treated with a 0.05% fluticasone propionate ointment, in an 18 month oral (gavage) study in mice administered fluticasone propionate at dose levels of up to 1 mg/kg/day. In a lifetime (2 years) snout-only inhalation study in rats, at dose levels of up to 57 μg/kg/day, there was an increase in the incidence of tumours in the mammary gland, liver and pancreas. These were not considered as evidence of tumorogenic effect of fluticasone propionate based on the absence of statistical support of an increase in incidence and the historical tumour data.

Local Tolerance
Little or no irritancy was observed following the application of ointment formulations containing up to 0.1% fluticasone propionate either as daily doses for 35 days to the skin of the rat or as single dose, non-occluded or occluded tests on intact or abraded guinea pig skin. Negligible irritancy was produced following the application of fluticasone propionate cream or ointment (containing up to 0.05% w/w fluticasone propionate) formulations as single occluded doses on intact and abraded skin and as a series of 4 daily repeated non-occluded doses on the intact skin of the guinea pig.

A single application of 0.05% w/w fluticasone propionate cream to abraded skin sites on rats did not affect the normal wound healing process.

Micronised fluticasone propionate was considered to be non-irritating in the rabbit eye when assessed using a modified Draize test and in the guinea pig split adjuvant test for evaluating contact sensitivity, results were completely negative.

PART III: CONSUMER INFORMATION

PrCutivate®
Fluticasone propionate

This leaflet is part III of a three-part "Product Monograph" published when CUTIVATE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CUTIVATE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What CUTIVATE® is used for:
CUTIVATE® is used to help relieve the redness and itchiness of certain skin problems in patients over 12 years of age.

What it does:

CUTIVATE® contains fluticasone propionate which belongs to a group of medicines called steroids. Steroids help to reduce the redness, swelling and itchiness of the skin .

"Topical steroids" mean they are put on the skin (and should not be confused with "anabolic steroids" which are taken as tablets or injections, and misused by some body builders).

When it should not be used:

Do not use CUTIVATE® if you are allergic to fluticasone propionate, other corticosteroids, or to any of the other ingredients in CUTIVATE® (see **What the nonmedical ingredients are**).

Do not use this cream for the following skin problems as it could make them worse, especially:

- Acne.
- Bacterial, fungal, viral skin infections (e.g., herpes simplex, chicken pox), tuberculosis skin infections, or a skin reaction following a recent vaccination.
- Itchiness of the skin which is not inflamed.
- Around the anus / genitals.
- Do not apply in or near the eye.
- Rosacea (a facial skin condition where the nose, cheeks, chin, forehead or entire face are unusually red, with or without tiny visible blood vessels, bumps (papules) or pus-filled bumps (pustules)).
- Dermatitis (rashes) around the mouth.

What the medicinal ingredient is:

Fluticasone propionate

What the nonmedicinal ingredients are:

Imidurea as a preservative. Your body can break down imidurea into formaldehyde that may cause redness and itchiness (see WARNINGS AND PRECAUTIONS).

Other nonmedicinal ingredients include propylene glycol, mineral oil, cetostearyl alcohol, polyoxyl 20 cetostearyl ether, isopropyl myristate, dibasic sodium phosphate, citric acid and purified water.

What dosage forms it comes in:

Cream, 0.05%

WARNINGS AND PRECAUTIONS

BEFORE you use CUTIVATE® talk to your doctor or pharmacist if:

- You ever had to stop using a similar medicine because you were allergic to it or it caused problems.
- You have been told that you are allergic to formaldehyde.
- You have any skin disease around a leg ulcer, use of a topical corticosteroid may increase the risk of an allergic reaction or an infection around the ulcer.
- You have other inflammatory skin diseases in the leg as a result of impaired circulation (stasis dermatitis).
- You are pregnant, think you could be pregnant, planning to become pregnant or breastfeeding a baby. If you do use CUTIVATE® when breastfeeding, do not apply CUTIVATE® on your breasts to ensure that the baby does not accidentally get CUTIVATE® in their mouth.
- You have problems with your kidney or liver.

If you are over 65 years of age, use CUTIVATE® with caution.

Only use CUTIVATE® for as long as your doctor recommends. If your condition does not improve within 2 to 4 weeks of treatment, speak to your doctor.

Do not use airtight dressings on treated areas of the skin.

Topical corticosteroids, when used over large areas, on sensitive areas such as the face, in skin-fold areas like the armpit and groin or broken skin, for prolonged periods, are more likely to be absorbed into the bloodstream and cause side effects.

CUTIVATE® should not be used on the face, or in skin fold areas, such as the groin or the armpit.

Avoid getting CUTIVATE® in the eye, or on other mucous membranes.

INTERACTIONS WITH THIS MEDICATION

Some drugs that may affect how CUTIVATE® works, or make it more likely that you will have side effects. Some of these medicines may include:

- Ritonavir (for HIV).
- Itraconazole (for fungal infections).

Tell your doctor or pharmacist about all your other medications, including medicines that you bought without a prescription and natural health products.

PROPER USE OF THIS MEDICATION

For topical use only and not for ophthalmic, oral or intravaginal use.

CUTIVATE® should not be used in children under the ages of 12 years old.

Unless used for treating hands, wash your hands again after using CUTIVATE®.

Allow time for CUTIVATE® to be absorbed before applying a moisturizer.

Usual dose:

Use CUTIVATE® as your doctor has prescribed for you. Check with your doctor or pharmacist if you are unsure how much or how often to use CUTIVATE®. Apply a thin layer once or twice a day (as your doctor has prescribed for you) and gently rub in, using only enough to cover the entire affected area.

You should not use CUTIVATE® more than you are told or over large body areas for a long time.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Apply CUTIVATE® as soon as you remember, then continue as before. Do not apply extra CUTIVATE® to make up for missed doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects will affect your skin and may affect other parts of your body if a sufficient amount of CUTIVATE® is absorbed through the skin and entered into your blood stream. Some side effects with CUTIVATE® may include:

Common: itching

Uncommon: local skin burning

If you experience local burning or itchiness, or your condition gets worse, there is no need to stop CUTIVATE®, but you should tell your doctor of any of these symptoms as soon as possible.

Side effects with the use of topical corticosteroid include:

- burning, itching, skin irritation, dryness, inflammation of hair follicles, abnormal hair growth
- stretch marks
- secondary infection, acne
- allergic contact dermatitis
- heat rash (miliaria)
- skin thinning, loss of skin color (hypopigmentation)

Serious side effects such as Cushing's syndrome may be associated with systemic absorption of topical corticosteroids (for example, from long-term, improper or excessive use). Symptoms include: increased weight, moon face / rounding of the face and obesity. Also, look out for delayed weight gain and slow growth in children. Other symptoms that may only show in blood tests or when your doctor gives you a medical examination are: decreased hormone cortisol levels in your blood, increased sugar levels in your blood or urine, high blood pressure, cloudy lens in the eye (cataract), increased pressure in the eye (glaucoma), as well as weakening of the bones through gradual mineral loss (osteoporosis) and additional tests may be needed after

your medical examination to confirm whether you have osteoporosis.

If you have psoriasis, you may get raised bumps with pus under the skin. This can happen very rarely during or after treatment and is known as pustular psoriasis.

Patients should report any signs of local or systemic adverse reactions to their doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Allergic reaction: wheeziness and tightness of chest, swelling of eyelids, face or lips, or develop skin lumps or hives or skin rash (e.g., red spots)			✓
Cushing's syndrome: associated with systemic absorption of topical corticosteroids (for example, from long-term, improper or excessive use).			✓

This is not a complete list of side effects. For any unexpected effects while taking CUTIVATE®*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store between 2° and 30°C. Do not freeze. Keep out of reach of children.

If your doctor decides to stop the treatment, do not keep any leftover cream unless your doctor tells you to.

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.stiefel.ca or by contacting the sponsor,

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