

New!

GlaxoSmithKline Consumer Healthcare

**R** **Cutivate<sup>®</sup> Cream 0.05%**  
**(fluticasone propionate)**

DIN 02089912

**Topical Anti-Inflammatory Corticosteroid**



**Available in Canada**  
**– Dec 2004**

***A New Treatment For Corticosteroid-Responsive Dermatoses With A Proven Safety Profile***

- Proven Efficacy In The Relief Of Inflammatory And Pruritic Dermatoses<sup>1</sup>
- Flexible, Patient Friendly BID or QD dosing for eczema<sup>1</sup>
- Favourable Safety Profile – adverse reactions were mild and self-limiting and included: pruritis, dryness, numbness of fingers, and burning<sup>1</sup>

Cutivate<sup>®</sup> Cream 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Cutivate<sup>®</sup> Cream 0.05% is not indicated in patients with a hypersensitivity to any of its components and is also contra-indicated in the treatment of rosacea, acne vulgaris, perioral dermatitis, primary cutaneous viral infections, perianal and genital pruritus, primarily infected skin lesions caused by infection with fungi or bacteria and dermatoses in children including dermatitis and diaper rash.

References: 1. Cutivate<sup>®</sup> Product Monograph 1999



Cream 15 g / 60 g

**Cutivate<sup>®</sup>**

## Product Monograph

### PrCUTIVATE®

#### (Fluticasone Propionate cream, 0.05%) Topical Anti-inflammatory Corticosteroid

#### Clinical Pharmacology

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 lipocortinase A, a phospholipase A<sub>2</sub> inhibitor 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 A<sub>2</sub>.

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 for 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.

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.

#### Indications and Clinical Use

CUTIVATE® (fluticasone propionate) Cream, 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Studies performed with CUTIVATE Cream, 0.05% have shown that it is in the medium range of potency as compared with other topical corticosteroids.

#### Contraindications

Fluticasone propionate cream, 0.05% is not indicated in patients with a hypersensitivity to any of the components. The preparation also contraindicated in the breast area, rosacea, acute varicella, primary and secondary cutaneous viral infections (i.e., herpes simplex, chickenpox), perianal and genital pruritus, primarily infected skin lesions caused by infection with fungi or bacteria and dermatoses in children, including dermatitis and diaper rash.

#### Warnings

Cutivate should not be used under occlusive dressing. Avoid prolonged application to the face since the face, more than other areas of the body, may exhibit drastic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematosus and severe eczema.

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye to avoid the risk of local infection or glaucoma.

#### PRECAUTIONS

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. Patients receiving a large dose of a potent topical steroid applied to a large surface area or under occlusive dressing should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, morning plasma cortisol, and urinary free cortisol tests.

Fluticasone propionate cream, 0.05% produced HPA axis suppression within seven days when used at a dose of 30 mg per day in diseased children. 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 patient persisted at this level for 48 days 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.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug to reduce the frequency of application or to substitute a less potent steroid. 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 corticosteroid therapy. For information on systemic supplementation, see prescribing information for those products.

Topical steroids may be hazardous in psoriasis for a number of reasons, including 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. In addition, the use of topical steroids in psoriasis may be associated with a low 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 patient persisted at this level for 48 days 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.

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Herpes simplex	0	1 (0.8%)
Impeligo	1 (0.8%)	0
Atopic dermatitis	1 (0.8%)	0
Eczema	1 (0.8%)	0
Exacerbation of eczema	4 (3.0%)	1 (0.8%)
Erythema	0	2 (1.6%)
Burning	0	2 (1.6%)
Stinging	0	1 (0.8%)
Skin irritation	6 (4.5%)	1 (0.8%)
Pruritus	2 (1.5%)	3 (2.3%)
Exacerbation of pruritus	4 (3.0%)	1 (0.8%)
Folliculitis	1 (0.8%)	1 (0.8%)
Blisters	0	1 (0.8%)
Dryness of skin	1 (0.8%)	1 (0.8%)

#### Symptoms and Treatment of Overdose

Overdose may cause the features of hypercorticism to appear. As with any corticosteroid, treatment should be discontinued if the symptoms of hypercorticism appear. Topically applied fluticasone propionate cream, 0.05% can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS)

#### Dosage and Administration

Eczema: Apply a thin film of CUTIVATE (fluticasone propionate) Cream to the affected skin areas once or twice daily. Rub in gently.  
Other Corticosteroid Responsive Dermatoses: Apply a thin film of CUTIVATE Cream 0.05% to the affected skin areas twice daily. Rub in gently.

#### PHARMACEUTICAL INFORMATION

##### Drug Substance

**Proprietary Name:** fluticasone propionate (BAN, INN, USAN)  
**Chemical Name:** 9-Fluoro-11beta-difluoro-18-hydroxy-16alpha-methyl-3-oxo-17alpha-propionyloxandrostano-4,13-diene-17beta-carboxylate  
**Structural Formula:**

**Molecular Formula:** C<sub>27</sub>H<sub>37</sub>F<sub>7</sub>O<sub>5</sub>  
**Molecular Weight:** 500.6  
**Description:** Fluticasone propionate is a white to off-white powder.  
**Solubility:** Fluticasone propionate is freely soluble in dimethyl sulfoxide and dimethylformamide, sparingly soluble in acetone, dichloromethane, ethyl acetate and chloroform, slightly soluble in methanol and 95% ethanol, and practically insoluble in water.

Fluticasone propionate decomposes without melting. Onset of decomposition occurs at about 225°C.

##### Melting Point:

Each gram of CUTIVATE (fluticasone propionate) Cream, 0.05% w/w contains fluticasone propionate 500 micrograms in a cream base. Non-medicinal ingredients include polyethylene glycol, mineral oil, cetostearyl alcohol, polyoxy 20 cetostearyl ether, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water and inurea as a preservative.

**Stability and Storage Recommendations**  
Store between 2° and 30°C.

#### AVAILABILITY OF DOSAGE FORMS

CUTIVATE (fluticasone propionate) Cream, 0.05% is supplied in 15 and 60 g tubes.

#### Information for the Consumer

### CUTIVATE CREAM

(fluticasone propionate)

**WHAT YOU SHOULD KNOW ABOUT CUTIVATE CREAM**  
Please read this leaflet carefully before you start to use your medicine. This provides a summary of the information available on your medicine. For further information or advice, ask your doctor or pharmacist.

**THE NAME OF YOUR MEDICINE**  
The name of your medicine is CUTIVATE cream. It contains fluticasone propionate. This medicine is one of a group of medicines called topical steroids. "Topical" means they are put on the skin. (They should not be confused with "anabolic" steroids misused by some body builders and taken as tablets or injections).

**HOW TO OBTAIN YOUR MEDICINE**  
This medicine can only be obtained with a prescription from a doctor.

**THE PURPOSE OF YOUR MEDICINE**  
Your doctor has prescribed this cream to treat an inflamed skin condition such as eczema, psoriasis or dermatitis.

**HOW YOUR MEDICINE WORKS**  
CUTIVATE cream is used to reduce the redness and itchiness of certain skin problems.

**IMPORTANT POINTS TO NOTE BEFORE USING YOUR MEDICINE**  
Have you ever had to stop using a similar medicine because you were allergic to it or it caused problems?

If the answer to this question is YES, tell your doctor or pharmacist as soon as possible if you have not already done so.  
Do not use this cream for any skin problems as it could make them worse. Eczema, psoriasis, skin infections (cold sores, herpes, impetigo, athlete's foot, chicken pox, ringworm, thrush), itchiness of the anus, itchiness of the genitals, conditions called rosacea and dermatitis around the mouth.

**THE USE OF THIS MEDICINE DURING PREGNANCY AND BREAST-FEEDING**  
Tell your doctor if you are pregnant or breast feeding a baby.

Your doctor may decide not to prescribe this medicine during the first three months of pregnancy or if you are breast feeding a baby. However, there may be circumstances when your doctor advises you differently.

**HOW TO USE YOUR MEDICINE**  
Use the cream as your doctor prescribed. If you are not sure how much to use or how often, ask your doctor or pharmacist.

Unless used for treating the hands wash them again after using the cream.  
You should not use more than you are told.  
CUTIVATE cream should not be used in children under 12 years of age.  
You should not use the cream on large areas of the body for a long time.  
Do not let the cream get into your eyes.

If your doctor has prescribed this cream for psoriasis, you should let your doctor review your progress at regular intervals, as such treatment needs careful supervision.

**AFTER USING YOUR MEDICINE**  
If you experience wheeziness and tightness of chest, swelling of eyelids, face or lips or develop skin lumps or hives, or skin rash (e.g. red spots), tell your doctor immediately. Do not use any more cream unless your doctor tells you to do so. He may decide to stop your treatment.

You may experience local burning or itchiness or your condition may get worse. There is no need to stop the cream, but you should tell your doctor of any of these symptoms as soon as possible.

Use of this cream for a long period of time on large areas may cause thinning of the skin or streaks in the skin. Streaking of the skin and changes in skin colour are more pronounced. Also, excessive hairiness of the skin or decreased colouring of the skin may be seen.

If you feel unwell or have any symptoms that you do not understand, you should contact your doctor as soon as possible.

**WHAT TO DO IF AN OVERDOSE IS USED**  
It is important to stick to the dose on the label of your medicine. Using more than this is unlikely to be dangerous unless a lot is used at all once. In that case, ask your doctor what to do.

**STORING YOUR MEDICINE**  
Keep your cream in a safe place where children cannot reach it. Your medicine may harm them.  
CUTIVATE cream should not be frozen.

**WHAT TO DO IF YOU STOP YOUR MEDICINE**  
If your doctor decides to stop the treatment, do not keep any leftover cream unless your doctor tells you to.

**WHAT IS IN YOUR MEDICINE**  
CUTIVATE cream contains 0.05% fluticasone propionate.

**A REMINDER**  
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.

**FURTHER INFORMATION**  
If you have any questions or are not sure about your medication, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. PLEASE DO NOT THROW IT AWAY until you have finished your medicine.

**Pharmacology**  
Fluticasone propionate was shown to be approximately twice as potent in topical

activity as budesonide 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 in 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 potentials of topically applied drug demonstrated that fluticasone propionate has an advantageous therapeutic index (>200 times that of bethamethasone 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 demonstrated 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 bethamethasone alcohol and fluocinolone acetonide using thymus involution, adrenal atrophy, and inhibition of carrageenin granuloma formation as assessments of systemic activity. Fluticasone propionate was equipotent with bethamethasone 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 bethamethasone alcohol and 100 times less potent than fluocinolone acetonide in mice.

After oral dosing in the rat, fluticasone propionate caused some thymus involution, adrenal atrophy and HPA axis suppression but was 6 to 18 times less potent than bethamethasone alcohol. In the mouse, oral fluticasone propionate is 60 to 200 times less potent than bethamethasone alcohol.

Fluticasone propionate caused a wide range of steroid hormone 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 ovariectomized rats and mice and also showed some anti-androgenic and anti-oestrogenic activity. With 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, dog and man 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 faeces, and evidence from bile duct-cannulated animals indicates that the major route of excretion is via the bile. Only minor excretion of radioactivity was observed in the urine, and 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 faeces 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 carboxylate group to yield the active 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 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.

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

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 ointment or cream formulations with or without occlusion. This was due to the fact that only 45 of the 45 volunteers and 45 of the fluticasone propionate ointment (a ten-fold higher concentration of ointment than that currently 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.

Single application studies have shown fluticasone propionate to have no potential to cause irritation, contact sensitization, photo toxicity or photo contact allergy, despite the aggressive nature of the dosing schedules employed. Fluticasone propionate ointment (0.05%) and cream (0.05% and 0.05%) preparations were tested at concentrations of 0.1 mL for up to 26 days in these specialised studies.

**Pharmacokinetics**  
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 low systemic activity. 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 faeces, 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.

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 9 hours, and the volume of distribution is approximately 292 L.

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.

The twice-daily application of 25 g of 0.05% fluticasone propionate ointment under occlusion for 5 days to healthy male volunteers resulted in maximum trough levels in the range of 0.22 to 0.77 ng/mL.

#### 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, subcutaneous and intravenous routes indicated a large margin of safety over the anticipated exposure of humans following the dermal application of cream preparations containing 0.05% fluticasone propionate. Systemic exposure following the dermal application of 0.05% cream would be 45 µg/kg, assuming human oral bioavailability of approximately 5% and the use in a 50 kg person of 90 g of cream in one day. The approximate LD<sub>50</sub> values are shown in the following table:

Species	Route	Approx. LD <sub>50</sub> (mg/kg)
Mouse	Oral	>1000
Rat	Oral	>1000
Mouse	Subcutaneous	>1000
Rat	Subcutaneous	>1000
Rat	Intravenous	>2
Rat	Inhalation	>166
Dog	Inhalation	>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-detectable cortical depletion of the adrenal glands in the rat.

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 ulcer lesions were seen. These observed changes are the expected response to a glucocorticoid shock of severity.

Intravenous 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 ulcer lesions were seen. These observed changes are the expected response to a glucocorticoid shock of severity.

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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 as follows:

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
Dog	Subcutaneous	10 µg/kg/day	35 days
Rat	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/ml/day	10 days
		9 mg/ml/day	44 days

\*Key: \* - maximum dose of fluticasone propionate administered.

Clinical observations were similar for all routes