ZOFLUT Cream (Fluticasone propionate)

Composition

ZOFLUT Cream contains:
Fluticasone Propionate,BP............................0.05% w/w
In a cream base........................................q.s.

Dosage Form

Topical cream

Pharmacology

► Pharmacodynamics

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic 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. Arachidonic acid is released from membrane phospholipids by phospholipase A2.
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, oestrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.
Studies performed on fluticasone propionate cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.
Fluticasone propionate has no unexpected hormonal effects and no overt, marked effects upon the central and peripheral nervous systems, the gastrointestinal system or the cardiovascular or respiratory systems.

► Pharmacokinetics

Absorption
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 enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Bioavailability is very low after topical or oral administration, due to limited absorption through the skin or from the gastrointestinal tract, and because of extensive first-pass metabolism.
In a human study of 12 healthy males receiving 12.5 g of fluticasone propionate cream, 0.05%, twice daily for 3 weeks, plasma levels were generally below the level of quantification (0.05 ng/mL). In another study of 6 healthy males administered 25 g of fluticasone propionate cream, 0.05%, under occlusion for 5 days, plasma levels of fluticasone ranged from 0.07 to 0.39 ng/mL.

In an animal study using radio labelled 0.05% fluticasone propionate cream and ointment preparations, rats received a topical dose of 1 g/kg for a 24-hour period. Total recovery of radio activity was approximately 80% at the end of 7 days. The majority of the dose (73%) was recovered from the surface of the application site. Less than 1% of the dose was recovered in the skin at the application site. Approximately 5% of the dose was absorbed systemically through the skin. Absorption from the skin continued for the duration of the study (7 days), indicating a long retention time at the application site.

**Distribution**

Following intravenous administration of 1 mg fluticasone propionate in healthy volunteers, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The apparent volume of distribution averaged 4.2 L/kg (range: 2.3–16.7 L/kg). The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transporting.

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

**Metabolism**

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

No metabolites of fluticasone propionate were detected in an in vitro study of radio labelled fluticasone propionate incubated in a human skin homogenate. The total blood clearance of systemically absorbed fluticasone propionate averages 1,093 mL/min (range: 618–1,702 mL/min) after a 1mg intravenous dose, with renal clearance accounting for less than 0.02% of the total. Fluticasone propionate is metabolized in the liver by cytochrome (CY) P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothioate grouping. This transformation occurs in one metabolic step to produce the inactive 17-β-carboxylic acid metabolite, the only known metabolite detected in humans, which has very weak glucocorticoid or anti-inflammatory activity. This metabolite has approximately 2,000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in humans.

**Excretion**

Following an intravenous dose of 1 mg in healthy volunteers, fluticasone propionate showed poly exponential kinetics and had an average terminal half-life of 7.2 hours (range: 3.2–11.2 hours).

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

In humans too, metabolic clearance is extensive, and elimination is consequently rapid. Thus, drug entering the systemic circulation via the skin will be rapidly inactivated. Oral bioavailability approaches zero, due to poor absorption and extensive first-pass metabolism. Therefore, systemic exposure to any ingestion of the topical formulation will be low.

**Indications**
Treatment of inflammatory dermatoses.

Adults

ZOFLUT Cream is a medium potent topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. These include the following:

- Atopic dermatitis
- Nummular dermatitis (discoid eczemas)
- Prurigo nodularis
- Psoriasis (excluding widespread plaque psoriasis)
- Lichen simplex chronicus (neurodermatitis) and lichen planus
- Seborrhoeic dermatitis
- Irritant or allergic contact dermatitis
- Discoid lupus erythematosus
- An adjunct to systemic steroid therapy in generalized erythroderma
- Insect bite reactions
- Miliaria (prickly heat)

Children

For children and infants aged 3 months and over who are unresponsive to lower potency corticosteroids, ZOFLUT Cream is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis under the supervision of a specialist. Expert opinion should be sought prior to the use of ZOFLUT Cream in other corticosteroid-responsive dermatoses in children. The safety and efficacy of drug use for longer than 4 weeks in this population has not been established.

Dosage And Administration

Creams are especially appropriate for moist or weeping surfaces.

Dosage for Adults, the Elderly, Children and Infants Aged 3 Months and Over

In atopic dermatitis, apply a thin film of ZOFLUT Cream to the affected skin areas once or twice daily. Rub in gently, using only enough cream to cover the entire affected area.

For other corticosteroid-responsive dermatoses, apply a thin film of ZOFLUT Cream to the affected skin areas twice daily. Rub in gently.

Apply for up to 4 weeks until improvement occurs, then reduce the frequency of application or change the treatment to a less potent preparation. Allow adequate time for absorption after each application before applying an emollient. Therapy with topical corticosteroids should be gradually discontinued once control is achieved and an emollient should be continued as maintenance therapy.

ZOFLUT Cream should not be used with occlusive dressings. ZOFLUT Cream should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressings.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical steroids, especially with potent preparations.

Duration of Treatment

Adults and the Elderly

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

Children Aged Over 3 Months
Children are more likely to develop local and systemic side effects of topical corticosteroids and, in general, require shorter courses and less potent agents than adults. Care should be taken when using fluticasone propionate to ensure the amount applied is the minimum that provides therapeutic benefit.

Children and Infants

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

### Contraindications

ZOFLUT Cream is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation. The following conditions should not be treated with fluticasone propionate:
- Untreated cutaneous infections
- Rosacea
- Acne vulgaris
- Perioral dermatitis
- Perianal and genital pruritus
- Pruritus without inflammation
- Dermatoses in infants below 3 months of age, including dermatitis and nappy rash

### Warnings And Precautions

#### General

Fluticasone propionate should be used with caution in patients with a history of local hypersensitivity to other corticosteroids. Local hypersensitivity reactions may resemble symptoms of the condition under treatment.

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 (hypercortisolism), hyperglycaemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary-free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application gradually, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency.

Risk factors for increased systemic effects are:
- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
Use on occluded areas of skin (e.g. on inter triginous areas or under occlusive dressings (in infants the nappy may act as an occlusive dressing)
Increasing hydration of the stratum corneum
Use on thin skin areas such as the face
Use on broken skin or other conditions where the skin barrier may be impaired

Fluticasone propionate cream, 0.05%, caused depression of A.M. plasma cortisol levels in 1 of 6 adult patients when used daily for 7 days in patients with psoriasis or eczema involving at least 30% of the body surface. After 2 days of treatment, this patient developed a 60% decrease from pretreatment values in the A.M. plasma cortisol level.

There was some evidence of corresponding decrease in the 24-hour urinary-free cortisol levels. The A.M. plasma cortisol level remained slightly depressed for 48 hours but recovered by day 6 of treatment.

Overt suppression of the HPA-axis (A.M. plasma cortisol less than 5 micrograms/dL) is very unlikely to result from therapeutic use of fluticasone propionate cream unless treating more than 50% of an adult’s body surface and applying more than 20 g per day.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in 2 of 43 paediatric patients aged 2 and 5 years old, who were treated for 4 weeks, covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis.
Paediatric patients may be more susceptible to systemic toxicity from equivalent doses due to an immature skin barrier and their larger skin surface to body mass ratios. The following local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, hypertrichosis, and miliaria.

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

Fluticasone propionate cream, 0.05%, may cause local cutaneous adverse reactions.

If irritation develops, fluticasone propionate cream, 0.05%, should be discontinued and appropriate therapy instituted. 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.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favourable response does not occur promptly, use of fluticasone propionate cream, 0.05%, should be discontinued until the infection has been adequately controlled.

Fluticasone propionate cream, 0.05%, should not be used in the presence of pre-existing skin atrophy and should not be used where infection is present at the treatment site.

Fluticasone propionate cream, 0.05%, should not be used in the treatment of rosacea and perioral dermatitis.

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 the impaired barrier function of the skin have been reported in some cases. If used in psoriasis, careful patient supervision is important.

Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes. If applied to the eyelids, care is needed to ensure that the preparation does not enter the eyes, as cataract and glaucoma might result from repeated exposure.
Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings. When using occlusive dressings, the skin should be cleansed before a fresh dressing is applied. Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

There have been no studies to investigate the effect of fluticasone propionate on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of topical fluticasone propionate.

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions as well as non-healing or worsening of skin condition.
- Parents of paediatric patients should be advised not to use this medication in the treatment of diaper dermatitis. Fluticasone propionate cream, 0.05%, should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing.
- This medication should not be used on the face, underarms or groin areas unless directed by a physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

### Drug Interactions

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids, leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

### Renal/Hepatic impairment

In case of systemic absorption (when application is over a large surface area for a prolonged period), metabolism and elimination may be delayed therefore increasing the risk of systemic toxicity. Therefore, the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

### Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Administration of fluticasone propionate cream, 0.05%, during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. The minimum quantity should be used for the minimum duration.

### Lactation

The safe use of topical corticosteroids during lactation has not been established. It is not known whether the topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Administration of fluticasone propionate during lactation should only be considered if
the expected benefit to the mother outweighs the risk to the infant. If used during lactation, fluticasone propionate should not be applied to the breasts to avoid accidental ingestion by the infant.

**Paediatric Use**

The safety and efficacy of drug use for longer than 4 weeks in this population has not been established. The safety and efficacy of fluticasone propionate cream, 0.05%, in paediatric patients below 3 months of age has not been established.

Parents of paediatric patients should be advised not to use this medication in the treatment of diaper dermatitis unless directed by the physician. Fluticasone propionate cream, 0.05%, should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing.

Adverse effects, including striae, have been reported with the use of topical corticosteroids in paediatric patients. HPA axis suppression, Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in paediatric patients receiving topical corticosteroids.

Manifestations of adrenal suppression in paediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

**Geriatric Use**

The adverse reactions reported in this population (>65 years of age) were similar to those reported by younger patients. Based on available data, no adjustment of dosage in geriatric patients is warranted.

**Undesirable Effects**

In controlled clinical trials of twice-daily administration, the total incidence of adverse reactions associated with the use of fluticasone propionate cream, 0.05%, was approximately 4%. These adverse reactions were usually mild, 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.

Two clinical studies compared once- to twice-daily administration of fluticasone propionate cream, 0.05%, for the treatment of moderate-to-severe eczema. The local drug-related adverse events for the 491 patients enrolled in both studies are shown in Table 1. In the study enrolling both adult and paediatric patients, the incidence of local adverse events in the 119 paediatric patients aged 1 to 12 years was comparable with the 140 patients aged 13 to 62 years.

An open-label HPA axis safety study enrolled 51 paediatric patients aged 3 months to 5 years, with moderate-to-severe eczema. Fluticasone propionate cream, 0.05%, was applied twice daily for 3–4 weeks over an arithmetic mean body surface area of 64% (range: 35–95%). The mean morning cortisol levels with standard deviations before treatment (pre-stimulation mean value = 13.76 ± 6.94 mcg/dL; post-stimulation mean value = 30.53 ± 7.23 mcg/dL) and at end-treatment (pre-stimulation mean value = 12.32 ± 6.92 mcg/dL; post-stimulation mean value = 28.84 ± 7.16 mcg/dL) showed little change. In 4.7% patients with end-treatment results, peak cortisol levels following cosyntropin stimulation testing were ≤18 μg/dL, indicating adrenal suppression. Follow-up testing after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis. Local drug-related adverse events were transient burning, resolving the same day it was reported; transient urticaria, resolving the same day it was reported; erythematous rash; dusky erythema, resolving within 1 month after cessation of fluticasone propionate cream, 0.05%; and telangiectasia, resolving within 3 months after stopping fluticasone propionate cream,
Adverse drug reactions (ADRs) are listed below by organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

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.

**Infections and Infestations**

Very rare: opportunistic infection

**Immune System Disorders**

Very rare: hypersensitivity

**Endocrine Disorders**

Very rare: HPA axis suppression:
- increased weight/obesity
- delayed weight gain/growth retardation in children
- cushingoid features (e.g. moon face, central obesity)
- decreased endogenous cortisol levels
- hyperglycaemia/glucosuria
- hypertension
- osteoporosis
- cataract
- glaucoma

**Skin and Subcutaneous Tissue Disorders**

Common: pruritus

Uncommon: local skin burning

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

The following localized adverse reactions have also been reported during post-approval use: skin discolouration, irritation, oedema/swelling, atrophy, contusion, dermatitis, pain, sepsis, haemorrhage, acneiform eruptions.

Systemic adverse events with fluticasone propionate cream, 0.05%, have also included the following: immunosuppression/Pneumocystis carinii pneumonia/leucopenia/thrombocytopenia; Cushing's syndrome; generalized body oedema/blurred vision; and acute urticarial reaction (oedema, urticaria, pruritus, and throat swelling).

**Overdosage**

Topically applied fluticasone propionate may be absorbed in sufficient amounts to produce systemic effects.
Acute overdosage is very unlikely to occur; however, in the case of chronic overdosage or misuse, the features of hypercortisolism may appear. In the event of overdose, fluticasone propionate should be withdrawn gradually by reducing the frequency of application, or by substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency. Further management should be as clinically indicated or as recommended by the National Poisons Centre, where available.

**Incomptability**

None reported.

**Storage And Handling Instructions**

Store below 25°C.

**Packaging Information**

ZOFLUT Cream.................................................................5 g and 10 g tube

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ZOFLUT Cream

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