SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cutivate Cream 0.05%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluticasone Propionate (micronised) 0.05% w/w

Excipients with known effect:
Cetostearyl Alcohol
Propylene Glycol
Imidurea

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TREATMENT OF INFLAMMATORY DERMATOSES

Adults:

Fluticasone propionate cream is a 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 generalised erythroderma
- Insect bite reactions
- Miliaria (prickly heat)

Children:

For children and infants aged three months and over who are unresponsive to lower potency corticosteroids, Cutivate 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 Cutivate Cream in other corticosteroid responsive dermatoses in children.

4.2 Posology and method of administration

Route of administration: Cutaneous

Adults, elderly, children and infants aged 3 months and over

Creams are especially appropriate for moist or weeping surfaces.

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice a day 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 continued as maintenance therapy.

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

Duration of treatment for adults and elderly

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

Children 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.

Duration of treatment for children and infants

When Cutivate 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.

Elderly

Clinical studies have not identified differences in responses between the elderly and younger patients. 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.

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.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

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 under three months of age, including dermatitis and nappy rash.

4.4 Special warnings and precautions for use

Fluticasone propionate should be used with caution in patients with a history of local hypersensitivity to other corticosteroids. Local hypersensitivity reactions (*see section 4.8*) may resemble symptoms of the condition under treatment.

Manifestations of hypercortisolism (Cushing's Syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency *(see section 4.8).*

Risk factors for increased systemic effects are:
- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin (e.g. on intertriginous areas or under occlusive dressings (in infants the nappy may act as an occlusive dressing)
- Increasing hydration of the stratum corneum
- Use on thin skin areas such as the face
- Use on broken skin or other conditions where the skin barrier may be impaired
- In comparison with adults, children and infants may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a greater surface area to body weight ratio compared with adults.

Children

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

Use in psoriasis
Topical steroids should be used with caution in psoriasis as rebound relapses, development of tolerance, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases. If used in psoriasis, careful patient supervision is important.

Application to the face
Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes.

Application to the eyelids
If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as cataract and glaucoma might result from repeated exposure.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Concomitant infection
Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate antimicrobial therapy.

Infection risk with occlusion
Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings. When using occlusive dressings, the skin should be cleansed before a fresh dressing is applied.

Chronic leg ulcers
Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Overt suppression of the HPA-axis (morning plasma cortisol less than 5 micrograms/dL) is very unlikely to result from therapeutic use of 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 contains the excipient imidurea, which releases traces of formaldehyde as a breakdown product. Formaldehyde may cause allergic sensitisation or irritation upon contact with the skin.

Fluticasone propionate cream contains the excipient cetostearyl alcohol which may cause local skin reactions (e.g. local dermatitis).

Healthcare professionals should be aware that if this product comes into contact with dressings, clothing and bedding, the fabric can be easily ignited with a naked flame. Patients should be warned of this risk and advised to keep away from fire when using this product.

Fluticasone propionate cream contains the excipient propylene glycol which may cause local skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

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

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (*see section 5.3*).
The relevance of this finding to humans has not been established; however, administration of fluticasone propionate 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.

Breast-feeding
The safe use of topical corticosteroids during lactation has not been established.

It is not known whether the topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk.

When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the 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.

Fertility
There are no data in humans to evaluate the effect of topical corticosteroids on fertility (*see section 5.3*).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and 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.

Post-Marketing Data

Infections and infestations
Very rare: Opportunistic infection.

Immune system disorders
Very rare: Hypersensitivity.

Endocrine disorders
Very rare: Hypothalamic-pituitary adrenal (HPA) axis suppression:
- Increased weight / obesity
- Delayed weight gain/growth retardation in children
- Cushingoid features (e.g. moon face, central obesity)
- Decreased endogenous cortisol levels
- Hyperglycaemia/glucosuria
- Hypertension
- Osteoporosis
- Cataract
- Glaucoma

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.

Eye disorders
Not known: Vision, blurred (see also section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmaceutical Services, Ministry of Health, CY-1475 Nicosia, Fax: + 357 22608649, Website: www.moh.gov.cy/phs (for Cyprus).

4.9 Overdose

Symptoms and Signs

Topically applied fluticasone propionate may be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the features of hypercortisolism may appear (*see section 4.8*).

Treatment
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: D07AC Corticosteroid, potent (Group III)

Topical corticosteroids, have anti-inflammatory, antipruritic, and vasoconstrictive properties.

They act as anti-inflammatory agents via multiple mechanisms to inhibit late phase allergic reactions including decreasing the density of mast cells, decreasing chemotaxis and activation of eosinophils, decreasing cytokine production by lymphocytes, monocytes, mast cells and eosinophils, and inhibiting the metabolism of arachidonic acid.

Fluticasone propionate is a glucocorticoid with high topical anti-inflammatory potency but low HPA-axis suppressive activity after dermal administration. It therefore has a therapeutic index which is greater than most of the commonly available steroids.

It shows high systemic glucocorticoid potency after subcutaneous administration but very weak oral activity, probably due to metabolic inactivation. *In vitro* studies show a strong affinity for, and agonist activity at, human glucocorticoid receptors.

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.

5.2 Pharmacokinetic properties

Pharmacokinetic data for the rat and dog indicate rapid elimination and extensive metabolic clearance. 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. 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.

Fluticasone propionate does not persist in any tissue, and does not bind to melanin. The major route of metabolism is hydrolysis of the S-fluoromethyl carbothioate group, to yield a carboxylic acid (GR36264), which has very weak glucocorticoid or anti-inflammatory activity. In all test animal species, the route of excretion of radioactivity is independent of the

route of administration of radiolabelled fluticasone propionate. Excretion is predominantly faecal and is essentially complete within 48 hours.

In man too, metabolic clearance is extensive, and elimination is consequently rapid. Thus drug entering the systemic circulation via the skin, will be rapidly inactivated. 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.

5.3 Preclinical safety data

Reproductive studies suggest that administration of corticosteroids to pregnant animals can result in abnormalities of foetal development including cleft palate/lip. However, in humans, there is no convincing evidence of congenital abnormalities, such as cleft palate or lip.

Studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and general reproductive performance revealed no special hazard for humans, other than that anticipated for a potent steroid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Paraffin
Cetostearyl Alcohol
Isopropyl Myristate
Cetomacrogol 1000
Propylene Glycol
Imidurea
Sodium Phosphate
Citric Acid Monohydrate
Purified Water

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

15 g collapsible internally-laquered, blind-end aluminium tube, with latex bands and closed with polypropylene cap.

6.6 Special precautions for disposal and other handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

16799

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 1996
Date of latest renewal: 21 March 2012

10. DATE OF REVISION OF THE TEXT

8 April 2019