National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

Topivate Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20g cream contains Betamethasone (as Betamethasone Valerate) 0.1%
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Aqueous Cream

4. Clinical particulars

4.1 Therapeutic indications

Betamethasone valerate is a potent topical corticosteroid indicated for adults, elderly and children over 1 year for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses. These include the following:

Atopic dermatitis (including infantile atopic dermatitis)

Nummular dermatitis (discoid eczema)

Prurigo nodularis

Psoriasis (excluding widespread plaque psoriasis)

Lichen simplex chronicus (neurodermatitis) and lichen planus

Seborrhoeic dermatitis

Irritant or allergic contact dermatitis

Discoid lupus erythematosus

Adjunct to systemic steroid therapy in generalised erythroderma

Insect bite reactions

4.2 Posology and method ofadministration

Route of administration: Cutaneous

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 daily 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.

In the more resistant lesions, such as the thickened plaques of psoriasis on elbows and knees, the effect of betamethasone valerate can be enhanced, if necessary, by occluding the treatment area with polythene film. Overnight occlusion only is usually adequate to bring about a satisfactory response in such lesions; thereafter, improvement can usually be maintained by regular application without occlusion.

If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated.

Therapy with betamethasone valerate 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 betamethasone valerate.

Recalcitrant dermatoses

Patients who frequently relapse

Once an acute episode has been treated effectively with a continuous course of topical corticosteroid, intermittent dosing (apply once a day twice a week without occlusion) may be considered. This has been shown to be helpful in reducing the frequency of relapse.

Application should be continued to all previously affected sites or to known sites of potential relapse. This regimen should be combined with routine daily use of emollients. The condition and the benefits and risks of continued treatment must be re-evaluated on a regular basis.

Paediatric population

Betamethasone valerate is contraindicated in children under one year of age.

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; therefore, courses should be limited to five days and occlusion should not be used.

Care should be taken when using betamethasone valerate to ensure the amount applied is the minimum that provides therapeutic benefit.

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 in the excipients listed in section 6.1.

The following conditions should not be treated with betamethasone valerate:

• Untreated cutaneous infections

o Rosacea

o Acne vulgaris

o Pruritus without inflammation

o Perianal and genital pruritus

o Perioral dermatitis

Betamethasone valerate is contraindicated in dermatoses in infants under one year of age, including dermatitis

4.4 Special warnings and precautions for use

Betamethasone valerate 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:

o Potency and formulation of topical steroid

o Duration of exposure

o Application to a large surface area

o 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)

o Increasing hydration of the stratum corneum

o Use on thin skin areas such as the face

o Use on broken skin or other conditions where the skin barrier may be impaired

o In comparison with adults, children 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.

Paediatric population

In infants and children under 12 years of age, treatment courses should be limited to five days and occlusion should not be used; long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.

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.

Use in Psoriasis

Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerances, 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; therefore, treatment courses should be limited to five days and occlusion should not be used.

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.

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.

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.

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 Pregnancy and Lactation

Fertility
There are no data in humans to evaluate the effect of topical corticosteroids on fertility.

Pregnancy
There are limited data from the use of betamethasone valerate 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 betamethasone valerate during pregnancy should only be considered if the expected benefit to the mother outweighs the 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 topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Administration of betamethasone valerate during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

If used during lactation betamethasone valerate should not be applied to the breasts to avoid accidental ingestion by the infant.

4.7 Effects on ability to drive and use machines
There have been no studies to investigate the effect of betamethasone valerate 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 betamethasone valerate.

4.8 Undesirable effects
Adverse drug reactions (ADRs) are listed below by MedDRA system 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.

Post-marketing data

Infections and Infestations

Very rare	Opportunistic infection

Immune System Disorders

Very rare	Hypersensitivity, generalised rash

Endocrine Disorders

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

	trichorrhexis

Skin and Subcutaneous Tissue Disorders

Common	Pruritus, local skin burning /skin pain
Very rare	Allergic contact dermatitis /dermatitis, erythema, rash, urticaria, pustular psoriasis, skin thinning* / skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms

General Disorders and Administration Site Conditions

Very rare	Application site irritation/pain

**Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.*

Eye disorders

Not known	Vision, blurred (see also section 4.4)

4.9 Overdose

Symptoms and signs
Topically applied betamethasone valerate 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 occur (*see section 4.8)*.

Treatment
In the event of overdose, betamethasone valerate 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 Corticosteroids, potent (group III)

Mechanism of action
Topical corticosteroids 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.

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

5.2 Pharmacokinetic properties

Absorption
Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

Distribution
The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary because circulating levels are well below the level of detection.

Metabolism
Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways

similar to systemically administered corticosteroids. They are metabolised, primarily in the liver.

Elimination
Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

5.3 Preclinical safety data

Reproductive toxicity
Subcutaneous administration of betamethasone valerate to mice or rats at doses ≥0.1 mg/kg/day or rabbits at doses ≥12 micrograms/kg/day during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

The effect on fertility of betamethasone valerate has not been evaluated in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitan Monostearate
Polysorbate 60
Synthetic Spermaceti
Cetostearyl Alcohol
Isopropyl Mystristate
Benzyl Alcohol
Deionised Water

6.2 Incompatibilities
None known.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30^{o}C.

6.5 Nature and contents of container
20gm collapsible aluminium tubes internally coated with an epoxy resin based lacquer and closed with a cap.

6.6 Special precautions for disposal
No special requirements.

7 . APPLICANT/MANUFACTURER
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