SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
PSODERM 0.05% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 g of cream contains:
Active substance:
Clobetasol 17-propionate ..... 0.5 mg
Excipients with known effect:
Chlorocresol ..... 0.75 mg
Cetostearyl alcohol ..... 84 mg
Propylene glycol ..... 475 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Cream.
White to off-white cream, homogeneous cream.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
PSODERM is a very potent topical corticosteroid indicated for adults, elderly, and children over 1 year for the short-term treatment of more resistant inflammatory and pruritic manifestations of conditions unresponsive to less potent corticosteroids. These include:
- Psoriasis (excluding widespread plaque psoriasis)
- Recalcitrant dermatoses
- Lichen planus
- Discoid lupus erythematosus
- Other skin conditions that do not respond satisfactorily to less potent steroids

4.2 Posology and method of administration
Posology/frequency and duration of administration

Clobetasol propionate belongs to the most potent class of topical corticosteroids (Group IV), and, as with all other topical corticosteroids, uncontrolled and prolonged use may result in serious side effects (see section 4.4). If treatment with a local corticosteroid is clinically justified beyond 4 weeks, a less potent corticosteroid treatment should be considered. Repeated but short-term courses of clobetasol propionate may be used to control exacerbations (see details below).

Method of administration
PSODERM cream is especially appropriate for moist or weeping surfaces.

Adults, elderly, and children over 1 year
Apply thinly and gently rub in, using only enough to cover the entire affected area once or twice a day until an apparent improvement occurs (in the more responsive conditions, this may be within a few days). Then reduce the frequency of application or change the treatment to a less potent medication.

Allow adequate time for absorption after each application before applying an emollient.

Repeated short courses of PSODERM may be used to control exacerbations.

In more resistant lesions, especially where there is hyperkeratosis, the effect of PSODERM 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. Improvement thereafter can usually be maintained by application without occlusion.

If the patient's condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated. Treatment should not be continued for more than 4 weeks. If prolonged treatment is necessary, a less potent medication should be used.

The maximum weekly dose should not exceed 50 g.

Once control is achieved, treatment with PSODERM should be gradually discontinued and an emollient continued as maintenance therapy.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of PSODERM.

Recalcitrant dermatoses:

Patients who frequently relapse

Once an acute episode has been treated effectively with a continuous course of topical corticosteroid, intermittent dosing (once daily, twice weekly, 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 or known sites of potential relapse. This application should be combined with routine daily use of emollients. The condition and the benefits and risks of continued treatment should be reassessed on a regular basis.

Application to the face:
Courses should be limited to five days if possible and occlusion should not be used.

Additional information on special populations

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 lowest amount should be used for the shortest duration to achieve the desired clinical benefit.

Pediatric patients
It is contraindicated in children under 1 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.

PSODERM is not recommended for use in pediatric patients unless required.

Care should be taken to apply the lowest amount at which therapeutic benefit is achieved.

Courses should be limited if possible to five days and reviewed weekly. Occlusion should not be used.

Geriatric patients
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 lowest amount should be used for the shortest duration to achieve the desired clinical benefit.

4.3 Contraindications

- The following conditions should not be treated with PSODERM:
  - Rosacea
  - Acne vulgaris
  - Perioral dermatitis
  - Perianal and genital pruritus
  - Untreated skin infections
  - Pruritus without inflammation
- It should not be used in patients with hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- It is contraindicated in dermatoses in children under one year of age, including dermatitis and nappy eruptions.

4.4 Special warnings and precautions for use

Clobetasol should be used with caution in patients with a history of local hypersensitivity to other corticosteroids or to any of the excipients in the preparation. Local hypersensitivity reactions may resemble symptoms of the diagnosed disease (see section 4.8).

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 discontinuation of the drug may lead to glucocorticosteroid insufficiency (see section 4.8).

Cases of serious osteonecrosis infections (including necrotizing fasciitis) and systemic immunosuppression (sometimes resulting in reversible Kaposi's sarcoma lesions) have been reported with long-term use of clobetasol propionate beyond the recommended doses (see section 4.2). In some cases, patients used concomitantly other potent oral/topical corticosteroids or immunosuppressors (e.g., methotrexate, mycophenolate mofetil). If treatment with local corticosteroids clinically exceeds 4 weeks, continuation with a less potent corticosteroid preparation should be considered.

<u>Risk factors for increased systemic effects are:</u>

- Formulation and potency of topical corticosteroids
- 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
- Children and infants may be more susceptible to systemic effects due to higher absorption compared to adults. This is because children have an immature skin barrier and a greater surface area to body weight ratio compared with adults.

<u>Pediatric patients</u>

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

Duration of treatment in children and infants
Children are more susceptible to develop atrophic changes with the use of topical corticosteroids. If PSODERM must be used in children, treatment should not exceed 5 days. 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. If it does enter the eye, the affected eye should be bathed in copious amounts of water.

Visual disturbances
Visual disturbance has been reported with systemic and/or 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 which have been reported after use of systemic and topical corticosteroids.

Application to the face
Application to the face is undesirable as this area is more susceptible to atrophic changes. Therefore, if used on the face, the treatment should be limited to 5 days.

Risk of infection with occlusion
Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by 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; rebound relapses, the development of tolerance, the risk of generalized pustular psoriasis, and the development of local and 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.

Chronic leg ulcer
Topical corticosteroids are sometimes used to treat 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.

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

PSODERM may cause allergic reactions due to the chlorocresol excipient it contains.

PSODERM may cause skin irritation due to the propylene glycol excipient it contains.

PSODERM may cause local skin reactions (e.g., contact dermatitis) due to the cetostearyl alcohol excipient it contains.

4.5 Interactions with other medicinal products and other forms of interaction
Concomitant use of CYP3A4 inhibitor drugs (e.g., ritonavir, itraconazole) has been shown to inhibit corticosteroid metabolism, 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.

Additional information on special populations
Not reported.

Pediatric patients
Not reported.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category is "C".

Women of child-bearing potential/Birth control (Contraception)
No special contraception is required for use in women of childbearing potential. It should not be used commonly, at high doses, and for long periods in women planning pregnancy.

Pregnancy
There are limited data from the use of clobetasol in pregnant women.
Topical administration of corticosteroids to pregnant animals can cause abnormalities in the fetal development (see section 5.3). The relevance of this finding to humans has not been established. The potential risk for humans is unknown. PSODERM should not be used during pregnancy unless necessary. Clobetasol should be used during pregnancy only if the expected benefit to the mother outweighs the risk to the fetus. If used, the minimum quantity should be used for the minimum duration.

Breastfeeding
Safety of using topical corticosteroids during lactation were not established. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Clobetasol should be used during lactation only if the expected benefit to the mother outweighs the risk to the infant. If used during lactation, clobetasol should not be applied to the breasts to avoid accidental ingestion by the infant.

Fertility
Animal studies revealed reproductive toxicity. However, the potential risk for humans is unknown. There are no data in humans to evaluate the effect of topical corticosteroids on fertility. Clobetasol administered subcutaneously to rats had no effect upon mating performance; however, fertility was decreased at the highest dose (see section 5.3).

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

4.8 Undesirable effects
Undesirable effects are presented with the following frequency categories: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from available data).

Post-marketing experience

Infections and infestations

Very rare: Opportunistic infections

Immune system disorders

Very rare: Local hypersensitivity

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, hyperglycemia/glucosuria, hypertension, increased weight/obesity, decreased endogenous cortisol levels, alopecia, trichorrhexis

Eye disorders

Very rare: Cataract, central serous chorioretinopathy, glaucoma

Unknown: Blurred vision (see. Section 4.4)

Skin and subcutaneous tissue disorders

Common: Pruritus, local skin burning, and skin pain

Uncommon: Skin atrophy*, striae*, telangiectasias*

Very rare: Skin thinning*, wrinkling*, skin dryness*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, allergic contact dermatitis/dermatitis, pustular psoriasis, erythema, rash, urticaria, acne

*Depends on local and systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression

General disorders and administration site conditions

Very rare: Irritation/Pain at the site of application

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose and treatment

Symptoms

Topically applied clobetasol propionate may be absorbed in sufficient amounts to produce systemic effects. Acute overdose is very unlikely to occur; however, in the case of chronic overdose or misuse, the signs of hypercortisolism may occur (see section 4.8).

Management

In the event of overdose, clobetasol propionate should be withdrawn by reducing the frequency of application or substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency. Subsequent treatment should be administered as clinically indicated or, where available, as recommended by the national poison center.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Corticosteroids, very potent (dermatological) (group IV)

ATC code : D07AD01

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 suppressing the metabolism of arachidonic acid.

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

5.2 Pharmacokinetic properties

General properties

Absorption

Topical corticosteroids are absorbed systematically from intact skin. The extent of percutaneous absorption of topical corticosteroids depends on many factors, such as the vehicle used and the integrity of the epidermal barrier. Occlusion, inflammation, and/or other dermal diseases may also increase percutaneous absorption.

Mean peak plasma clobetasol propionate concentrations of 0.63 ng/ml occurred in one study eight hours after the second application (13 hours after an initial application) of 30 g clobetasol propionate 0.05% ointment to normal individuals with healthy skin. Following the application of a second dose of 30 g clobetasol propionate cream 0.05% mean peak plasma concentrations were slightly higher than the ointment and occurred 10 hours after application. In a separate study, mean peak plasma concentrations of approximately 2.3 ng/ml and 4.6 ng/ml occurred respectively in patients with psoriasis and eczema three hours after a single application of 25 g clobetasol propionate 0.05% ointment.

Distribution

Use of pharmacodynamic endpoints for assessing systemic exposure of topical corticosteroids is necessary due to the fact that circulating levels are well below the level of detection.

Biotransformation

Once absorbed through skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids, primarily in the liver.

Elimination

Excreted via kidneys. Also, some corticosteroids and their metabolites are excreted in the bile.

5.3 Preclinical safety data

Carcinogenesis/Mutagenesis

Carcinogenesis

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Genotoxicity

Clobetasol propionate was not mutagenic in a range of *in vitro* bacterial cell assays.

Reproductive Toxicology

Fertility

In fertility studies, subcutaneous administration of clobetasol propionate to rats at doses of 6.25 to 50 micrograms/kg/day produced no effects on mating, and fertility was only decreased at 50 micrograms/kg/day.

Pregnancy
Subcutaneous administration of clobetasol propionate to mice (≥ 100 micrograms/kg/day), rats (400 micrograms/kg/day) or rabbits (1 to 10 micrograms/kg/day) during pregnancy produced fetal abnormalities including cleft palate and intrauterine growth retardation.

In the rat study, where some animals were allowed to litter, developmental delay was observed in the F1 generation at ≥ 100 micrograms/kg/day and survival was reduced at 400 micrograms/kg/day. No treatment-related effects were observed in F1 reproductive performance or in the F2 generation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Chlorocresol
Cetostearyl alcohol
Glycerol monostearate
Polyethylene glycol 400 monostearate
Beeswax substitute
Sodium citrate anhydrous
Citric acid monohydrate
Propylene glycol
Purified water

6.2 Incompatibilities
No data is available.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and contents of the container
The packaging material is an aluminum tube and twist-off cap.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MA HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER
2015/19

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