SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ENSTILAR® CUTANEOUS FOAM, 50 microgram/0,5 mg/g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of cutaneous foam contains 50 micrograms of calcipotriol (as monohydrate) and 0,5 mg of betamethasone (as dipropionate).

Excipient with known effect

Butylhydroxytoluene (E321) 0,005 % *m/m*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous foam.

After spraying, a white to off-white foam is formed.

The foam has the appearance of a non-expanding foam that gradually collapses after spraying.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of psoriasis vulgaris in adults.

4.2 Posology and method of administration

Posology

Flare treatment

ENSTILAR should be applied to the affected area once daily. The recommended treatment period is 4 weeks. If it is necessary to continue or restart treatment after this period, treatment should be continued after medical review and under regular supervision.

Long-term maintenance treatment

Patients who have responded at 4 weeks' treatment using ENSTILAR once daily are suitable for long-term maintenance treatment. ENSTILAR should be applied twice weekly on two non-consecutive days to areas previously affected by psoriasis vulgaris. Between applications there should be 2-3 days without ENSTILAR treatment.

If signs of a relapse occur, flare treatment, as described above, should be re-initiated.

Maximum dose

The daily maximum dose of ENSTILAR should not exceed 15 g, i.e. one 60 g can should last for at least 4 days of treatment. A total of 15 g corresponds to the amount administered from the can if the actuator is fully depressed for approximately one minute. A two-second application delivers approximately 0,5 g. As a guide 0,5 g of foam should cover an area of skin roughly corresponding to the surface area of an adult hand.

If using other topical products containing calcipotriol in addition to ENSTILAR, the total dose of all calcipotriol containing medicines should not exceed 15 g per day.

The total body surface area treated should not exceed 30 %.

Special populations

Renal and hepatic impairment

The safety and efficacy of ENSTILAR in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population

The safety and efficacy of ENSTILAR in children below 18 years have not been

established. Currently available data in children aged 12 to 17 years are described in sections 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration

For cutaneous use.

The can should be shaken for a few seconds before use. ENSTILAR should be applied by spraying while holding the can at least 3 cm from the skin. The foam can be sprayed holding the can in any orientation except horizontally.

ENSTILAR should be sprayed directly onto each affected skin area and rubbed gently.

If used on the scalp, ENSTILAR should be sprayed into the palm of the hand and then applied to affected scalp areas with the fingertips. Hair washing instructions are provided in the leaflet.

The hands should be washed after using ENSTILAR (unless ENSTILAR is used to treat the hands) to avoid accidentally spreading to other parts of the body as well as unintended medicine absorption on the hands. Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. It is recommended not to take a shower or bath immediately after application of ENSTILAR. Let the foam remain on the scalp and/or skin during the night or during the day.

4.3 Contraindications

- Hypersensitivity to Calcipotriol and Betamethasone or to any of the excipients listed in section 6.1.
- ENSTILAR is contraindicated in erythrodermic and pustular psoriasis.
- Due to the content of calcipotriol, ENSTILAR is contraindicated in patients with known disorders of calcium metabolism (see section 4.4).
- Due to the content of corticosteroid, ENSTILAR is contraindicated in the following conditions if present in the treatment area: Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis, perioral

dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea ,ulcers and wounds (see section 4.4).

- ENSTILAR is contraindicated in patients with severe hepatic disorders or severe renal insufficiency.
- Safe use of ENSTILAR during human pregnancy and lactation has not been established. Corticosteroids have been shown to be teratogenic in animals following dermal application. As these medicines are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore, ENSTILAR should not be used during pregnancy.

4.4 Special warnings and precautions for use

Effects on endocrine system

Adverse reactions found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impaired glycaemic control of diabetes mellitus may occur also during topical corticosteroid treatment due to systemic absorption.

Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. Application on large areas of damaged skin, or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of corticosteroids (see section 4.8).

A borderline decrease in cortisol response to a adrenocorticotropic hormone (ACTH) was observed in subjects at 28 and 56 weeks of treatment.

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 a 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.

Effects on calcium metabolism

Due to the content of calcipotriol in ENSTILAR, hypercalcaemia may occur. Serum calcium is normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the maximum daily dose of ENSTILAR (15 g) is not exceeded (see section 4.2).

Local adverse reactions

ENSTILAR contains a potent group III-steroid and concurrent treatment with other steroids on the same treatment area must be avoided.

The skin of the face and genitals is very sensitive to corticosteroids. The medicine should not be used in these areas.

The patient must be instructed in correct use of ENSTILAR to avoid application and accidental transfer to the face, mouth, and eyes. Hands must be washed after each application to avoid accidental transfer to these areas as well as unintended medicine absorption on the hands.

Concomitant skin infections

If lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if infection worsens, treatment with ENSTILAR should be discontinued (see section 4.3).

Discontinuation of treatment

When treating psoriasis with topical corticosteroids, such as ENSTILAR, there may be a risk of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

Long-term use

Long-term use of corticosteroids may increase the risk of local and systemic adverse reactions. Treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated use

There is no experience with the use of ENSTILAR in guttate psoriasis.

Adverse reactions to excipients

ENSTILAR contains butylhydroxytoluene (E321) as an excipient, which may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

Concurrent treatment and UV exposure

There is limited experience with the use of this medicine on the scalp. Studies on combination products containing the same active ingredients in ointment and gel formulations are available, but there is limited experience with the combination of ENSTILAR with other topical anti-psoriatic products at the same treatment area, with systemic anti-psoriatic medicines, or with phototherapy.

During ENSTILAR treatment, patients should limit or avoid excessive exposure to either natural or artificial sunlight.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with ENSTILAR.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are no adequate data from the use of ENSTILAR in pregnant women. When administered orally in animals, studies of calcipotriol have not shown teratogenic effects, though reproductive toxicity has been shown (see section 5.3). Studies in animals with glucocorticoids have shown reproductive toxicity (see section 5.3), but a number of epidemiological studies (less than 300 pregnancy outcomes) have not revealed congenital anomalies among infants born to women treated with corticosteroids during pregnancy. The potential risk for humans is uncertain. ENSTILAR is contraindicated in pregnancy (see section 4.3).

Breastfeeding

Betamethasone passes into breast milk, but risk of an adverse reaction in the infant is very small with therapeutic doses. There are no data on the excretion of calcipotriol in breast milk. Caution should be exercised when prescribing ENSTILAR to women who breastfeed. The patient should be instructed not to use ENSTILAR on the breast when breastfeeding.

Fertility

Studies in rats with oral doses of calcipotriol or betamethasone dipropionate demonstrated no impairment of male and female fertility (see section 5.3). There are no data on human fertility.

4.7 Effects on ability to drive and use machines

ENSTILAR has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The estimation of the frequency of adverse reactions is based on a pooled analysis of data from clinical studies.

The most frequently reported adverse reactions during treatment are application site reactions.

Adverse reactions are listed by MedDRA SOC and the individual adverse reactions are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

- More frequent', 'very common' and 'common' ≡ 'frequent'
- 'Single reports' or 'isolated reports', 'uncommon', 'rare', 'very rare' ≡ 'less frequent'
- Not known (cannot be estimated from the available data)

Tabulated list of adverse reactions

System organ class	Frequency	Adverse reactions
Infections and infestations	Less frequent	Skin infection*******, folliculitis, furuncle
Blood and lymphatic system disorders	Less frequent	Ecchymosis
Immune system disorders	Less frequent	Hypersensitivity
Endocrine disorders	Less frequent	Hirsutism, cushings syndrome
Metabolism and nutrition disorders	Less frequent	Hypercalcaemia*, hypokalaemic syndrome
Nervous system disorders	Less frequent	Hyperaesthesia, numbness in fingers
Eye disorders	Not known	Vision blurred**, Posterior subscapular cataracts
Vascular disorders	Less frequent	Hypertension
Gastrointestinal disorder	Less frequent	Gastric ulcer
Skin and subcutaneous tissue disorders	Frequent	Skin exfoliation, pruritus, rash******, burning sensation of the skin
	Less frequent	Skin hypopigmentation, Skin atrophy, exacerbation of psoriasis, dermatitis, erythema, purpura or ecchymosis, skin irritation, pustular psoriasis, skin striae, photosensitivity reaction, acne, dry skin
	Not known	Hair colour changes***

Musculoskeletal and connective tissue disorders	Less frequent	Protein depletion
General disorders and administration site conditions	Less frequent	Rebound effect Application site pruritus Application site irritation Application site pain**** Application site pigmentation changes, Oedema
	Not known	Application site erythema*****

* Mild hypercalcaemia has been observed.

** See section 4.4.

*** Transient discolouration of the hair at scalp application site, to a yellowish colour in white or grey hair, has been reported for calcipotriol and betamethasone combination products.

**** Application site burning is included in application site pain.

***** Based on post-marketing experience.

****** Various types of rash reactions such as exfoliative rash, rash papular and rash pustular have been reported.

******* Skin infections including bacterial, fungal and viral skin infections have been reported.

Paediatric population:

No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed. A total of 106 adolescent subjects were treated in one open-label clinical trial. See section 5.1 for further details regarding this trial.

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone, respectively:

Calcipotriol:

Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, psoriasis aggravated, photosensitivity and hypersensitivity reactions, including very rare cases of angioedema and facial oedema.

Systemic effects after topical use may appear very rarely causing hypercalcaemia or hypercalciuria (see section 4.4).

Betamethasone (as dipropionate):

Local reactions can occur after topical use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation, and colloid milia.

When treating psoriasis with topical corticosteroids, there may be a risk of generalised pustular psoriasis.

Systemic reactions due to topical use of corticosteroids are rare in adults; however, they can be severe. Adrenocortical suppression, cataract, infections, impaired glycaemic control of diabetes mellitus, and increase of intra-ocular pressure can occur, especially after long-term treatment. Systemic reactions occur more frequently when applied under occlusion (plastic, skin folds), when applied onto large skin areas, and during long-term treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Usage above the recommended dose may cause elevated serum calcium which subsides when treatment is discontinued. The symptoms of hypercalcaemia include polyuria, constipation, muscle weakness, confusion, and coma.

Excessive prolonged use of topical corticosteroids may result in adrenocortical suppression which is usually reversible. Symptomatic treatment may be indicated.

In case of chronic toxicity the corticosteroid treatment must be discontinued gradually.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.13.8.1 Preparations for psoriasis.

Pharmacotherapeutic group: Antipsoriatics. Other antipsoriatics for topical use, Calcipotriol, combinations. ATC Code: D05AX52.

Mechanism of action

ENSTILAR combines the pharmacological effects of calcipotriol hydrate as a synthetic vitamin D3 analogue and betamethasone dipropionate as a synthetic corticosteroid.

In psoriasis, vitamin D and its analogues act mainly to inhibit keratinocyte proliferation and induce keratinocyte differentiation. The underlying antiproliferative mechanism of vitamin D in keratinocytes involves the induction of the growth inhibitory factor transforming growth factor-β and of cyclin-dependent kinase inhibitors, with subsequent growth arrest in the G1 phase of the cell cycle plus down-regulation of the two proliferation factors early growth response-1 and polo-like kinase-2.

In addition, vitamin D has an immunomodulatory effect, suppressing activation and differentiation of Th17/Th1 cells while inducing a Th2/Treg response.

In psoriasis, corticosteroids suppress the immune system, particularly pro-inflammatory cytokines and chemokines, thereby inhibiting T-cell activation. At the molecular level, corticosteroids act via the intracellular glucocorticoid receptor and the anti-inflammatory function is due to transrepression of pro-

inflammatory transcription factors such as nuclear factor κB, activator protein-1, and interferon regulatory factor-3.

In combination, calcipotriol monohydrate and betamethasone dipropionate promote greater anti-inflammatory and anti-proliferative effects than either component alone.

Pharmacodynamic effects

Short-term data

Under maximum use conditions, in subjects with extensive psoriasis on the body and scalp treated for up to 4 weeks, adrenal response to ACTH was determined by measuring serum cortisol levels. None of 35 subjects had suppressed serum cortisol levels at 30 or 60 minutes post ACTH stimulation. Thus it appears that for ENSTILAR, the risk of adrenal suppression is low when applied to extensive psoriasis vulgaris for 4 weeks. Similarly, there was no indication of abnormal calcium metabolism following application of ENSTILAR to extensive psoriasis vulgaris for 4 weeks.

Long-term data

The adrenal response to ACTH challenge was evaluated in adult subjects with moderate to severe psoriasis vulgaris involving at least 10 % of the body surface area. The subjects were randomised to receive ENSTILAR or foam vehicle twice weekly for up to 52 weeks (long-term maintenance treatment). Subjects experiencing a relapse were treated with ENSTILAR once daily for 4 weeks, then continued randomised treatment.

The trial results were in line with a low risk of adrenal suppression in subjects with extensive psoriasis (BSA 10-30 %) who use ENSTILAR twice weekly and as outlined for up to 52 weeks. There was no clinically relevant effect on the calcium metabolism in this trial.

Clinical efficacy and safety

Short-term data

The efficacy of once daily use of ENSTILAR has been investigated in three randomised, double-blind or investigator-blind, 4-week clinical trials including more than 1,100 subjects with psoriasis on the body

(also scalp in one of the trials) of at least mild severity according to the Physician's Global Assessment of disease severity (PGA).

ENSTILAR demonstrated treatment success (defined as "clear" or "almost clear" for subjects with at least moderate disease and clear for subjects with mild disease at baseline according to the PGA) on the body at week 4, in approximately 45 % to 54,6 % of the patients. Responses were observed across all baseline disease severities.

In one trial, that included subjects with scalp involvement, treatment success (PGA) on the scalp at week 4 was achieved in 53 % of patients.

Improvements were also observed in itch and itch-related sleep loss, with reductions evident from Day 3 and maintained throughout the treatment period. In addition, quality-of-life outcomes, measured by validated questionnaires (DLQI and EQ-5D-5L), demonstrated statistically significantly greater improvement compared to vehicle.

Long-term data

The efficacy and safety of treatment with ENSTILAR was investigated in a randomised, double-blind vehicle-controlled trial (Trial Four). Subjects were treated once daily with open-label ENSTILAR for 4 weeks and responders were then randomised to receive ENSTILAR (long-term maintenance treatment) or foam vehicle twice weekly for up to 52 weeks. Subjects in both treatment arms experiencing a relapse were treated once daily with ENSTILAR for 4 weeks, and those responding then continued randomised treatment.

Subjects on long-term maintenance treatment with ENSTILAR had longer time to first relapse, greater proportion of days in remission during the trial, and fewer relapses than subjects using foam vehicle.

Paediatric population

The safety of ENSTILAR was evaluated in a 4-week, uncontrolled, open-label study in 106 adolescents (12–17 years) with scalp and body psoriasis. No cases of hypercalcaemia or clinically relevant effects on calcium metabolism were observed.

No clinical manifestations on the adrenal function were detected by the ACTH challenge test.

5.2 Pharmacokinetic properties

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised.

The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate showed that the kidney and liver had the highest level of radioactivity.

The extent of percutaneous absorption of the two active ingredients following topical application of ENSTILAR was determined in the HPA axis trial in subjects with extensive psoriasis vulgaris (see section 5.1). Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in most samples from 35 patients treated once daily for 4 weeks for extensive psoriasis involving the body and scalp. Calcipotriol was quantifiable at some time point in 1 subject, betamethasone dipropionate in 5 subjects and metabolites of calcipotriol and betamethasone dipropionate were detectable in 3 and 27 subjects, respectively.

5.3 Preclinical safety data

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction toxicity studies with long-term oral administration of corticosteroids to rats, prolonged gestation and prolonged and difficult labour were detected. Moreover, reduction in offspring survival, body weight and body weight gain was observed. There was no impairment of fertility. The relevance for humans is unknown.

Calcipotriol has shown maternal and foetal toxicity in rats and rabbits when given by the oral route at doses of 54 µg/kg/day and 12 µg/kg/day, respectively. The foetal abnormalities observed with concomitant maternal toxicity included signs indicative of skeletal immaturity (incomplete ossification of

the pubic bones and forelimb phalanges, and enlarged fontanelles) and an increased incidence of supernumerary ribs.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Dermal carcinogenicity studies with calcipotriol and betamethasone dipropionate in mice and oral carcinogenicity studies in rats revealed no special risk to humans.

In a local tolerability study in minipigs, ENSTILAR caused mild to moderate skin irritation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid paraffin

Polyoxypropylene stearyl ether

All-rac-α-tocopherol

White soft paraffin

Butylhydroxytoluene (E321)

Butane

Dimethyl ether

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: 6 months.

6.4 Special precautions for storage

Store at or below 30 °C

Caution:

Extremely flammable aerosol.

Pressurised container: May burst if heated.

Protect from sunlight.

Do not expose to temperatures exceeding 50 °C.

Do not pierce or burn, even after use.

Do not spray on an open flame or other ignition source.

Keep away from sparks, open flames and other ignition sources.

No smoking.

6.5 Nature and contents of container

Aluminium can with a polyamide-imide inner lacquer, equipped with a continuous valve and actuator.

The can contains 60 g of foam, not including the amount of propellants.

Pack sizes: 60 g and 2 x 60 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

58/13.8.1/0038

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

To be updated