SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Calcipotriol/Betamethason Sandoz 50 microgram/g + 0,5 mg/g, zalf

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of ointment contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Ointment.

Off white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy in adults.

4.2 Posology and method of administration

Posology
[Nationally completed name] ointment should be applied to the affected area once daily.

The recommended treatment period is 4 weeks. There is experience with repeated courses of [Nationally completed name] up to 52 weeks. If it is necessary to continue or restart treatment after 4 weeks, treatment should be continued after medical review and under regular medical supervision.

When using calcipotriol containing medicinal products, the maximum daily dose should not exceed 15 g. The body surface area treated with calcipotriol containing medicinal products should not exceed 30 % (see section 4.4).

Special populations

Renal and hepatic impairment

The safety and efficacy of [Nationally completed name] ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of [Nationally completed name] ointment 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, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

[Nationally completed name] ointment should be applied to the affected area. In order to achieve optimal effect, it is not recommended to take a shower or bath immediately after application of [Nationally completed name] ointment.

4.3 Contraindications

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

[Nationally completed name] ointment is contraindicated in erythrodermic, exfoliative and pustular psoriasis.
Due to the content of calcipotriol [Nationally completed name] ointment is contra-indicated in patients with known disorders of calcium metabolism (see section 4.4).

Due to the content of corticosteroid [Nationally completed name] is contraindicated in the following conditions:
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).

4.4 Special warnings and precautions for use

Effects on endocrine system

[Nationally completed name] ointment contains a potent group III steroid and concurrent treatment with other steroids must be avoided.
Adverse reactions found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic 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).

In a study in patients with both extensive scalp and extensive body psoriasis using a combination of high doses of [Nationally completed name] gel (scalp application) and high doses of [Nationally completed name] ointment (body application), 5 of 32 patients showed a borderline decrease in cortisol response to adrenocorticotropic hormone (ACTH) challenge after 4 weeks of treatment (see section 5.1).

Effects on calcium metabolism
Due to the content of calcipotriol, hypercalcaemia may occur if the maximum daily dose (15 g) is exceeded. Serum calcium is normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are followed. Treatment of more than 30 % of the body surface should be avoided (see section 4.2).

Local adverse reactions
[Nationally completed name] contains a potent group III-steroid and concurrent treatment with other steroids on the same treatment area must be avoided. Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas. The patient must be instructed in correct use of the medicinal product 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.

Concomitant skin infections
When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if infection worsens, treatment with corticosteroids should be stopped (see section 4.3).

Discontinuation of treatment
When treating psoriasis with topical corticosteroids there may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

Long-term use
With long-term use there is an increased risk of local and systemic corticosteroid adverse reactions. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated uses
There is no experience with the use of [Nationally completed name] in guttate psoriasis.

Concurrent treatment and UV exposure
There is limited experience for the use of this medicinal product on the scalp. [Nationally completed name] ointment for body psoriasis lesions has been used in combination with [Nationally completed name] gel for scalp psoriasis lesions, but there is limited experience of combination of [Nationally completed name] with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During [Nationally completed name] treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UVR only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3).

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with [Nationally completed name].

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of [Nationally completed name] in pregnant women. 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. Therefore, during pregnancy, [Nationally completed name] should only be used when the potential benefit justifies the potential risk.

Breastfeeding
Betamethasone passes into breast milk but risk of an adverse effect on the infant seems unlikely with therapeutic doses. There are no data on the excretion of calcipotriol in breast milk. Caution should be exercised when prescribing [Nationally completed name] ointment to women who breast-feed. The patient should be instructed not to use [Nationally completed name] on the breast when breast-feeding.

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

4.7 Effects on ability to drive and use machines

[Nationally completed name] has no or negligible influence on the ability to drive and to use machines.

4.8 Undesirable effects

The estimation of the frequency of adverse reactions is based on a pooled analysis of data from clinical studies including post-authorisation safety studies and spontaneous reporting.

The most frequently reported adverse reactions during treatment are various skin reactions, like pruritus and skin exfoliations.

Pustular psoriasis and hypercalcaemia have been reported.
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.

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)

Infections and infestations	
Uncommon ≥1/1,000 to <1/100	Skin infection* Folliculitis
Rare ≥1/10,000 to <1/1,000	Furuncle
Immune system disorders	
Rare ≥1/10,000 to <1/1,000	Hypersensitivity
Metabolism and nutrition disorders	
Rare ≥1/10,000 and to <1/1,000	Hypercalcaemia
Eye disorders	
Not known	Vision, blurred (see also section 4.4), chorioretinopathy
Skin and subcutaneous tissue disorders	
Common ≥1/100 to < 1/10	Skin exfoliation Pruritus
Uncommon ≥1/1,000 to <1/100	Skin atrophy Exacerbation of psoriasis Dermatitis Erythema Rash** Purpura or ecchymosis Skin burning sensation Skin irritation
Rare ≥1/10,000 to <1/1,000	Pustular psoriasis Skin striae Photosensitivity reaction Acne Dry skin

General disorders and administration site conditions	
Uncommon ≥1/1,000 to <1/100	Application site pigmentation changes Application site pain***
Rare ≥1/10,000 to <1/1,000	Rebound effect

*Skin infections including bacterial, fungal and viral skin infections have been reported.
**Various types of rash reactions such as exfoliative rash, rash popular and rash pustular have been reported.
***Application site burning is included in application site pain

Paediatric population:
In an uncontrolled open study, 33 adolescents aged 12-17 years with psoriasis vulgaris were treated with calcipotriol and betamethasone ointment for 4 weeks to a maximum of 56 g per week. No new adverse events were observed and no concerns regarding systemic corticosteroid effect were identified. The size of this study does however not allow firm conclusions regarding the safety profile of calcipotriol and betamethasone ointment in children and adolescents.

In another uncontrolled clinical trial with 7 subjects aged 12 to 17 years no adverse reactions were reported. See section 5.1 for further details regarding the trial.

In this limited sample, no clinically relevant differences have been observed between the safety profiles of calcipotriol and betamethasone cream in adult and adolescent populations.

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, eczema, 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, impact on the metabolic 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 on large areas and during long term treatment (see 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 national reporting system listed in Appendix V.

4.9 Overdose

Use 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 suppress the pituitary-adrenal functions resulting in secondary adrenal insufficiency which is usually reversible. In such cases symptomatic treatment is indicated.
In case of chronic toxicity the corticosteroid treatment must be discontinued gradually.
It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of [Nationally completed name] ointment weekly (corresponding to a daily dose of approximately 34 g) for 5 months (maximum recommended dose 15 g daily) developed Cushing's syndrome during treatment and then pustular psoriasis after abruptly stopping treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Calcipotriol is a vitamin D analogue. In vitro data suggests that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.
Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppresive properties, however, without curing the underlying condition. Through occlusion the effect can be enhanced due to increased penetration of the stratum corneum. The incidence of adverse events will increase because of this. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

A multi-centre, randomised, double-blind, parallel-group phase III study have been conducted to investigate the efficacy, safety, and tolerability of a generic calcipotriol-betamethasone ointment formulation compared to Daivobet® and vehicle in the treatment of adult patients with chronic stable plaque psoriasis. A total number of 444 patients started double-blind treatment. The patients were

randomised to either the generic calcipotriol-betamethasone ointment (test), Daivobet® ointment (reference), or company's ointment formulation (placebo/vehicle) in a ratio of 4:4:1. The study medication was self-administered by the patient once daily for 4 weeks.
Primary efficacy endpoint was defined as mean percent change from baseline in modified PASI score at the end of 4-week treatment. The confirmatory analysis of the primary endpoint comparing test vs. reference treatment, showed that the test product is equivalent to the reference.
The confirmatory analysis of the primary endpoint for the comparison of the test product to placebo/vehicle, showed that the test product is superior over its vehicle.
The results obtained for the secondary endpoints confirmed the findings obtained for the primary endpoint. After 4 weeks of treatment the test product was significantly superior to placebo regarding all secondary endpoints.
Local tolerance was assessed by comparing type, number and severity of lesional/perilesional adverse reactions. Twelve patients experienced 17 cutaneous AEs with at least possible relationship to study medication (5 AEs in 4 patients treated with test drug, and each 6 AEs in each 4 patients treated with reference drug and placebo/vehicle formulation, respectively). All patients with cutaneous adverse events with at least possible relationship to study medication recovered completely. The overall tolerability of the test medication was comparable to the reference drug.
The evaluation of safety parameters (change in albumin-corrected serum calcium levels, change in total amount of cortisol excreted in 24-hour urine, the results of clinical examination, laboratory examination, and vital signs) provided no evidence for any safety concern.
The trial proved the therapeutic equivalence of the test product (Calcipotriol-Betamethasone Sandoz) to the reference drug (Daivobet®), and the superiority of the test product to placebo/vehicle, while providing no indication for safety concerns.

The confirmatory analysis of the primary endpoint comparing test vs. reference treatment, showed that the test product is ***therapeutically*** equivalent to the reference.

A safety study in 634 psoriasis patients has investigated repeated courses of calcipotriol and betamethasone ointment used once daily as required, either alone or alternating with calcipotriol ointment, for up to 52 weeks, compared with calcipotriol ointment used alone for 48 weeks after an initial course of calcipotriol and betamethasone ointment. Adverse drug reactions were reported by 21.7 % of the patients in the calcipotriol and betamethasone ointment group, 29.6 % in the calcipotriol and betamethasone ointment/calcipotriol ointment alternating group and 37.9 % in the calcipotriol group. The adverse drug reactions that were reported by more than 2 % of the patients in the calcipotriol and betamethasone ointment group were pruritus (5.8 %) and psoriasis (5.3 %). Adverse events of concern possibly related to long-term corticosteroid use (e.g. skin atrophy, folliculitis, depigmentation, furuncle and purpura) were reported by 4.8 % of the patients in the calcipotriol and betamethasone ointment group, 2.8 % in the calcipotriol and betamethasone ointment/calcipotriol alternating group and 2.9 % in the calcipotriol group.

Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis, using up to 106 g per week combined calcipotriol and betamethasone gel and calcipotriol and betamethasone ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6 %) after 4 weeks of treatment and in 2 of 11 patients (18.2 %) who continued treatment until 8 weeks. In all cases, the

serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients. With regard to HPA suppression, therefore, this study shows some evidence that very high doses of calcipotriol and betamethasone gel and ointment may have a weak effect on the HPA axis.

Paediatric population
The adrenal response to ACTH challenge was measured in an uncontrolled 4-week study in 33 adolescents aged 12-17 years with body psoriasis who used up to 56 g per week of calcipotriol and betamethasone ointment. No cases of HPA axis suppression were reported. No hypercalcaemia was reported but one patient had a possible treatment related increase in urinary calcium.

The findings from the above trial were also confirmed in another trial including 7 adolescent subjects aged 12 to 17 years with extensive psoriasis involving 10.5-16% of the body surface area (including scalp). Treatment consisted of once daily application of calcipotriol and betamethasone cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 8 was 27.2 g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism.

5.2 Pharmacokinetic properties

Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from calcipotriol and betamethasone ointment is less than 1 % of the dose (2.5 g) when applied to normal skin (625 cm2) for 12 hours.
Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Absorption through damaged skin is approx. 24 %.

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. Protein binding is approx. 64 %. Plasma elimination half-life after intravenous application is 5-6 hours. Due to the formation of a depot in the skin elimination after dermal application is in order of days.
Betamethasone is metabolised especially in the liver, but also in the kidneys to glucuronide and sulfate esters. 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, respectively, showed that the kidney and liver had the highest level of radioactivity.

Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients treated for 4 or 8 weeks with both calcipotriol and betamethasone gel and calcipotriol and betamethasone ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients.

Paediatric population

In a study including 7 adolescent patients (6 provided PK data) treated with calcipotriol and betamethasone cream formulation, calcipotriol and its metabolite MC1080 were below the lower limit of quantification in all plasma samples at Week 4. Betamethasone dipropionate were below the lower limit of quantification in all plasma samples at Week 4. The metabolite, betamethasone 17-propionate (B17P), was quantifiable in 3 of 6 (50%) subjects.

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.

A dermal carcinogenicity study with calcipotriol in mice and an oral carcinogenicity study in rats revealed no special risk to humans.

Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.

A dermal carcinogenicity study in mice and an oral carcinogenicity study in rats revealed no special risk of betamethasone dipropionate to humans. No photocarcinogenicity study has been performed with betamethasone dipropionate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

All rac-α-tocopherol (E307)
Oleyl alcohol
Paraffin light liquid
Paraffin white soft

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening: 1 year.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.
For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

Ointment is filled in the container with aluminium/epoxyphenol tubes with polyethylene or polypropylene screw caps.

Pack sizes:
Tubes containing 15g,30g, 60g and 120g of ointment.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 117920

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 20 januari 2016
Datum van laatste verlening: 14 december 2020

10. DATE OF REVISION OF THE TEXT

Laatst gedeeltelijke wijziging betreft rubriek 7: 8 februari 2024