

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calcipotriol/Betamethasone 50 microgram/g + 0.5 mg/g gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Butylhydroxytoluene (E321) up to 270 micrograms/g gel

Castor oil, hydrogenated 16.7 mg/g gel

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel

An almost clear, colourless to slightly off-white gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Topical treatment of scalp psoriasis in adults.

Topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris in adults.

4.2 Posology and method of administration

Posology

Calcipotriol/Betamethasone should be applied to affected areas once daily. The recommended treatment period is 4 weeks for scalp areas and 8 weeks for "non-scalp" areas. If it is necessary to continue or restart treatment after this period, 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).

If used on the scalp

All the affected scalp areas may be treated with Calcipotriol/Betamethasone gel. Usually an amount between 1 g and 4 g per day is sufficient for treatment of the scalp (4 g corresponds to one teaspoon).

Special populations

Renal and hepatic impairment

The safety and efficacy of Calcipotriol/Betamethasone gel in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population

The safety and efficacy of Calcipotriol/Betamethasone in children and adolescents below 18 years have not been established. Currently available data in adolescents aged 12 to 17 years are described in section 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration

For cutaneous use.

The gel should not be applied directly to the face or eyes. In order to achieve optimal effect, it is not recommended to take a shower or bath, or to wash the hair in case of scalp application, immediately after application of Calcipotriol/Betamethasone. The gel should remain on the skin during the night or during the day.

When using the tube

The tube should be shaken before use and the gel applied to the affected area.
The hands should be washed after use.

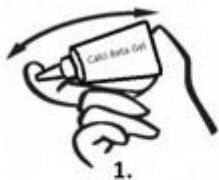
Instructions for proper use

- The medicinal product should only be used on the psoriasis but not on skin which does not have psoriasis
- The tube should be shaken before use and the cap should be removed
- The gel should be squeezed onto a clean finger or directly onto the area affected by psoriasis
- The medicinal product should be applied to the affected area with the fingertips, and it should be gently rubbed in until the area affected by psoriasis is covered by a **thin** layer of gel
- The treated skin area should not be bandaged, tightly covered or wrapped
- The hands should be well washed after using Calcipotriol/Betamethasone. This will avoid accidentally spreading the gel to other parts of the body (especially the face, mouth and eyes)
- If some gel accidentally gets on normal skin near the psoriasis, it should be wiped off if it spreads too far
- In order to achieve optimal effect, it is recommended not to take a shower or bath immediately after application of Calcipotriol/Betamethasone gel
- After applying the gel, contact with textiles which are easily stained by grease (e.g. silk) should be avoided.

In case of scalp psoriasis

- Before Calcipotriol/Betamethasone is applied to the scalp, the hair should be combed to remove any loose scales. The head should be tilted to make sure Calcipotriol/Betamethasone does not run onto the face. It may help to part the hair before Calcipotriol/Betamethasone is used. Calcipotriol/Betamethasone should be applied to the affected area with the fingertips and be gently rubbed in.

Washing the hair before application of Calcipotriol/Betamethasone is not necessary.



1. Tube should be shaken before use.



2. A drop of Calcipotriol/Betamethasone should be applied to fingertip.



3. Calcipotriol/Betamethasone gel should be applied directly where the raised plaque can be felt and rubbed in on the skin.

Depending on the affected area 1-4 g (up to 1 teaspoon) is normally enough.

In order to achieve optimal effect, it is recommended that the hair is not washed immediately after application of Calcipotriol/Betamethasone. Calcipotriol/Betamethasone should remain on the scalp during the night or during the day. When washing hair after application the following instructions might be useful:



A mild shampoo should be applied to the dry hair, especially to those areas where the gel was applied.

The shampoo should be left on the scalp for a couple of minutes before washing.

The hair should be washed as usual.

If necessary, steps 4-6 should be repeated once or twice.

Duration of treatment

- The gel should be used once a day. It may be more convenient to use the gel in the evening
- The normal initial treatment period is 4 weeks for scalp areas and 8 weeks for non-scalp areas
- The physician may decide on a different treatment period
- The physician may decide on repeated treatment
- Not more than 15 grams in one day should be used.

If other calcipotriol containing medicinal products are used, the total amount of calcipotriol medicinal products must not exceed 15 grams per day, and the area treated should not exceed 30% of the total body surface.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Calcipotriol/Betamethasone is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Due to the content of calcipotriol, Calcipotriol/Betamethasone is contraindicated in patients with known disorders of calcium metabolism (see section 4.4).

Due to the content of corticosteroid, Calcipotriol/Betamethasone 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

Calcipotriol/Betamethasone 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 Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel (scalp application) and high doses of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination ointment (body application), 5 of 32 patients showed a borderline decrease in cortisol response to adrenocorticotrophic hormone (ACTH) challenge after 4 weeks of treatment (see section 5.1).

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, hypercalcaemia may occur if the maximum daily dose (15 g) is exceeded. Serum calcium is normalized 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

Calcipotriol/Betamethasone 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 generalized 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 use

There is no experience with the use of Calcipotriol/Betamethasone in guttate psoriasis.

Concurrent treatment and UV exposure

Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination ointment for body psoriasis lesions has been used in combination with Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel for scalp psoriasis lesions, but there is limited experience of combination of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During Calcipotriol/Betamethasone 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).

Adverse reactions to excipients

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

Calcipotriol/Betamethasone contains castor oil, hydrogenated as an excipient, which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed with Calcipotriol/Betamethasone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel 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, Calcipotriol/Betamethasone should only be used when the potential benefit justifies the potential risk.

Breast-feeding

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 Calcipotriol/Betamethasone to women who breast-feed. The patient should be instructed not to use Calcipotriol/Betamethasone 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

Calcipotriol/Betamethasone has no or negligible influence on the ability to drive and 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-authorization safety studies and spontaneous reporting.

The most frequently reported adverse reaction during treatment is pruritus.

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)

Not known (cannot be estimated from available data)

| | |
|---|--|
| Infections and infestations | |
| Uncommon | Skin infection* Folliculitis |
| Immune system disorders | |
| Rare | Hypersensitivity |
| Eye disorders | |
| Uncommon | Eyeirritation |
| Not known | Vision blurred** |
| Skin and subcutaneous tissue disorders | |
| Common | Pruritus |
| Uncommon | Exacerbation of psoriasis Dermatitis Erythema Rash*** Acne Skin burning sensation Skin irritation Dry skin |
| Rare | Skin striae Skin exfoliation |
| Not | Hair colour changes**** |

| | |
|---|----------------------------|
| known | |
| General disorders and administration site conditions | |
| Uncommon | Application site pain***** |
| Rare | Rebound effect |

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

** See section 4.4

*** Various types of rash reactions such as rash erythematous and rash pustular have been reported.

**** Transient discolouration of the hair at scalp application site, to a yellowish colour in white or grey hair, has been reported.

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

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 generalized 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).

Paediatric population

No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed.

A total of 216 adolescent subjects were treated in three open label clinical trials.

See section 5.1 for further details regarding the trials.

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 HPRC Pharmacovigilance, website: www.hpra.ie.

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 Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination 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 suggest 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 immunosuppressive 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. In general, the mechanism of the anti-inflammatory activity of the topical steroids is unclear.

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 + betamethasone 50 micrograms/g + 0.5 mg/g combination gel and Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination 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 + betamethasone 50 micrograms/g + 0.5 mg/g combination gel and ointment may have a weak effect on the HPA axis.

The efficacy of once daily use of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel was investigated in two randomized, double-blind, 8-week clinical studies including a total of more than 2,900 patients with scalp psoriasis of at least mild severity according to the Investigator's Global Assessment of disease severity (IGA). Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and (in one of the studies) the gel vehicle alone, all used once daily. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel was statistically significantly more effective than the comparators. Results for speed of onset based on similar data at week 2 also showed Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel to be statistically significantly more effective than the comparators.

| % of patients with absent or very mild disease | Betamethasone dipropionate and Calcipotriol combination gel (n=1,108) | Betamethasone dipropionate (n=1,118) | Calcipotriol (n=558) | Gel vehicle (n=136) |
|--|---|--------------------------------------|----------------------|---------------------|
| week 2 | 53.2 % | 42.8 % ¹ | 17.2 % ¹ | 11.8 % ¹ |
| week 8 | 69.8 % | 62.5 % ¹ | 40.1 % ¹ | 22.8 % ¹ |

¹ Statistically significantly less effective than Betamethasone dipropionate and Calcipotriol combination gel (P<0.001)

The efficacy of once daily use of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel on non-scalp regions of the body was investigated in a randomized, double-blind, 8-week clinical study including 296 patients with psoriasis vulgaris of mild or moderate severity according to the IGA. Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone, all used once daily. Primary response criteria were controlled disease according to the IGA at week 4 and week 8. Controlled disease was defined as 'clear' or 'minimal disease' for patients with moderate disease at baseline or 'clear' for patients with mild disease at baseline. The percentage change in Psoriasis Severity and Area index (PASI) from baseline to week 4 and week 8 were secondary response criteria.

| % of patients with controlled disease | Betamethasone dipropionate and Calcipotriol combination gel (n=126) | Betamethasone dipropionate (n=68) | Calcipotriol (n=67) | Gel vehicle (n=35) |
|---------------------------------------|---|-----------------------------------|---------------------|--------------------|
| week 4 | 20.6 % | 10.3 % ¹ | 4.5 % ¹ | 2.9 % ¹ |
| week 8 | 31.7 % | 19.1 % ¹ | 13.4 % ¹ | 0.0 % ¹ |

¹ Statistically significantly less effective than Betamethasone dipropionate and Calcipotriol combination gel (P<0.05)

| Mean percentage reduction in PASI (SD) | Betamethasone dipropionate and Calcipotriol combination gel (n=126) | Betamethasone dipropionate (n=68) | Calcipotriol (n=67) | Gel vehicle (n=35) |
|--|---|-----------------------------------|--------------------------|--------------------------|
| week 4 | 50.2 (32.7) | 40.8 (33.3) ¹ | 32.1 (23.6) ¹ | 17.0 (31.8) ¹ |
| week 8 | 58.8 (32.4) | 51.8 (35.0) | 40.8 (31.9) ¹ | 11.1 (29.5) ¹ |

¹ Statistically significantly less effective than Betamethasone dipropionate and Calcipotriol combination gel (P<0.05)

Another randomized, investigator-blinded clinical study including 312 patients with scalp psoriasis of at least moderate severity according to the IGA investigated use of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel once daily compared with Daivonex Scalp solution twice daily for up to 8 weeks. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel was statistically significantly more effective than Daivonex Scalp solution.

| | | |
|--|---|---------------------------------|
| % of patients with absent or very mild disease | Betamethasone dipropionate and Calcipotriol combination gel (n=207) | Daivonex Scalp solution (n=105) |
| week 8 | 68.6 % | 31.4 % ¹ |

¹ Statistically significantly less effective than Betamethasone dipropionate and Calcipotriol combination gel (P<0.001)

A randomized, double-blind long-term clinical study including 873 patients with scalp psoriasis of at least moderate severity (according to the IGA) investigated the use of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel compared with calcipotriol in the gel vehicle. Both treatments were applied once daily, intermittently as required, for up to 52 weeks.

Adverse events possibly related to long-term use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference in the percentages of patients experiencing such adverse events between the treatment groups (2.6 % in the Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel group and 3.0 % in the calcipotriol group; P=0.73). No cases of skin atrophy were reported.

The efficacy of once daily use of Calcipotriol/Betamethasone in the treatment of mild to moderate plaque-type psoriasis was investigated in a randomized, double-blind, 8-week clinical study including 283 subjects (0155/2018). Comparators were gel vehicle alone and Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel (Daivobet® gel). Therapeutic equivalence of Calcipotriol/Betamethasone with Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel (Daivobet® gel) could be concluded based on equivalent mean % change from baseline in PASI at Week 4/Day 29 for both treatments. Superiority of Calcipotriol/Betamethasone compared to gel vehicle was demonstrated based on the higher primary efficacy variable mean % change from baseline in PASI at Week 4/Day 29.

| Relative change from baseline PASI [%] at Week 4 / Day 29 | Calcipotriol/Betamethasone (N=123) | Daivobet® (N=121) | Generic Vehicle (N=39) |
|---|------------------------------------|-------------------|------------------------|
| Mean ± SE | -58.1 ± 2.2 | -59.6 ± 2.3 | -21.8 ± 4.2 |
| 95%-CI | -62.5, -53.7 | -64.42, -55.3 | -30.0 -13.5 |
| Mean difference ¹ ± SE | | 1.7 ± 3.2 | -36.6 ± 4.7 |
| Mean difference ¹ 95%-CI | | -4.6, 7.9 | -45.7, -27.0 |
| Conclusions ^{2,3} | | Equivalence | Superiority |

¹ Difference of relative change vs. Calcipotriol/Betamethasone gel, determined as Calcipotriol/Betamethasone gel minus Daivobet® gel and Calcipotriol/Betamethasone gel minus Generic vehicle gel, respectively

² Equivalence of Calcipotriol/Betamethasone gel and Daivobet® gel concluded, if the Mean difference 95%-confidence interval is included entirely within the equivalence range of -15% to +15%.

³ Superiority of Calcipotriol/Betamethasone gel vs. Generic vehicle gel concluded, if the upper limit of the Mean difference 95%-confidence interval is negative, i.e. does not include zero.

Paediatric population

Scalp

Effects on calcium metabolism were investigated in two uncontrolled open 8-week studies including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

Scalp and body

Effects on calcium metabolism were investigated in one uncontrolled open 8-week trial in 107 adolescents aged 12-17 years with scalp and body psoriasis who used up to 114.2 g per week of Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 31 patients; five patients showed a decrease in cortisol response to ACTH challenge where 2 of the 5 patients showed only borderline decreases. Four of the patients showed decrease after 4 weeks of treatment and 2 showed decrease after 8 weeks including 1 patient showing a decrease at both periods. These events were mild, without clinical manifestations, and reversible.

5.2 Pharmacokinetic properties

The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel is comparable to Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination ointment formulation 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 metabolized. 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 metabolized 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 + betamethasone 50 micrograms/g + 0.5 mg/g combination gel and Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination 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.

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 were 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.

In local tolerability studies in rabbits, Calcipotriol + betamethasone 50 micrograms/g + 0.5 mg/g combination gel caused mild to moderate skin irritation and a slight transient irritation of the eye.

Environmental risk assessment studies have shown that betamethasone may pose a risk for aquatic compartment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, liquid
Polyoxypropylene stearyl ether
Castor oil, hydrogenated

Butylhydroxytoluene (E321)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening: 6 months.

6.4 Special precautions for storage

Do not refrigerate.

6.5 Nature and contents of container

White cylindrical HDPE tube with white PP screw cap. The tube is placed in a carton.

Pack sizes:

1 tube of 30 g

1 tube of 60 g

Multipacks containing 60 g (2 tubes of 30 g), and 120 g (2 tubes of 60 g)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Str. 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER

PA1983/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th June 2021

10 DATE OF REVISION OF THE TEXT