SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dalonev 50 micrograms/g + 0.5 mg/g ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:

Butylhydroxytoluene (E321) 50 micrograms/g ointment

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ointment.

Off-white to yellow.

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

Calcipotriol/Betamethasone ointment should be applied to the affected area once daily.

The recommended treatment period is 4 weeks. There is experience with repeated courses of Calcipotriol/Betamethasone ointment 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 Calcipotriol/Betamethasone ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population

The safety and efficacy of Calcipotriol/Betamethasone ointment in children below 18 years have not been established. Currently available data in children 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

Calcipotriol/Betamethasone 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 Calcipotriol/Betamethasone ointment.

4.3 Contraindications

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

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

Due to the content of corticosteroid Calcipotriol/Betamethasone ointment 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 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 calcipotriol+betamethasone dipropionate gel (scalp application) and high doses of calcipotriol+betamethasone dipropionate 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

Calcipotriol/Betamethasone ointment 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 use

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

Concurrent treatment and UV exposure

There is limited experience for the use of this medicinal product on the scalp. Calcipotriol+betamethasone dipropionate ointment for body psoriasis lesions has been used in combination with calcipotriol+betamethasone dipropionate gel for scalp psoriasis lesions, but there is limited experience of combination of calcipotriol+betamethasone dipropionate ointment with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During Calcipotriol/Betamethasone ointment 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.

Adverse reactions to excipients

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

Topical steroid withdrawal syndrome

Long term use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.

The label will state strong steroid.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Calcipotriol/Betamethasone ointment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Calcipotriol/Betamethasone ointment 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 ointment 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 ointment to women who breast-feed. The patient should be instructed not to use Calcipotriol/Betamethasone ointment 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 ointment 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-authorisation safety studies and spontaneous reporting. The most frequently reported adverse reactions during treatment are various skin reactions, like pruritus and skin exfoliation.

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.

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 to <1/1,000)	Hypercalcaemia
Eye disorders	
Not known (cannot be estimated from the available data)	Vision, blurred (see also section 4.4)
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 papular 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+betamethasone dipropionate 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/Betamethasone ointment in children and adolescents.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 dipropionate 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.

5.1 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. Betamethasone is classed as a potent corticosteroid. 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. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.
A safety study in 634 psoriasis patients has investigated repeated courses of calcipotriol+betamethasone dipropionate 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+betamethasone dipropionate ointment. Adverse drug reactions were reported by 21.7 % of the patients in the calcipotriol+betamethasone dipropionate ointment group, 29.6 % in the calcipotriol+betamethasone dipropionate ointment/ calcipotriol ointment alternating group and 37.9 % in the calcipotriol ointment group. The adverse drug reactions that were reported by more than 2 % of the patients in the calcipotriol+betamethasone dipropionate 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+betamethasone dipropionate ointment group, 2.8 % in the calcipotriol+betamethasone dipropionate ointment/ calcipotriol ointment alternating group and 2.9 % in the calcipotriol ointment 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+betamethasone dipropionate gel and calcipotriol+betamethasone dipropionate 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 dipropionate gel and ointment may have a weak effect on the HPA axis.

<u>Paediatric population</u>
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+betamethasone dipropionate 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.

5.2 Pharmacokinetic properties

Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone is less than 1 % of the dose (2.5 g) when applied to normal skin (625 cm^2) 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+betamethasone dipropionate gel and calcipotriol+betamethasone dipropionate 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 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

Liquid paraffin

Polyoxypropylene stearyl ether (contains butylhydroxytoluene (E321))

White soft paraffin (contains all-rac-α-Tocopherol)

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After first opening: 1 year

6.4 Special precautions for storage

Do not store above 25 °C.

Do not refrigerate.

6.5 Nature and contents of container

Aluminium/epoxyphenol tubes with polyethylene screw cap.

Pack sizes: 15 g, 30 g, 35 g, 50 g, 60 g, 100 g, 100 g (as bundle pack 2 x 50 g), 120 g and 120 g (as bundle pack 2 x 60 g).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Mibe Pharma UK Ltd
4 Coleman Street, 6th Floor
London
United Kingdom
EC2R 5AR

8 MARKETING AUTHORISATION NUMBER(S)

PL 49452/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/11/2023

10 DATE OF REVISION OF THE TEXT

20/06/2025