Calcibet Ointment

Calcipotriol 50mcg/g and Betamethasone 0.5mg/g

Composition
Each 1g contains
Calcipotriol monohydrate ..... 52.2μg (50μg as Calcipotriol)
Betamethasone dipropionate ..... 0.643mg (0.5mg as Betamethasone)

Excipients
White Petrolatum, Liquid Paraffin, Phenoxyethyl Caprylate, Tocopherol Acetate

Dosage Form
Ointment

Product Description
A pale yellow or yellow ointment

Pharmacodynamics
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.

Pharmacokinetics
Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Absorption through damaged skin is approximately 24%. Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate-are rapidly and extensively metabolized. Protein binding is approximately 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.

Indication
Initial topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy.

Recommended Dose
CALCIBET Ointment should be applied to the affected areas once daily. The recommended treatment period is 4 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 15g. The body surface area treated with calcipotriol containing medicinal products should not exceed 30%. In order to achieve optimal effect, it is not recommended to take a shower or bath immediately after application of the ointment.
Special populations
Renal and hepatic impairment
The safety and efficacy of CALCIBET Ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.
Paediatric population
The safety and efficacy of CALCIBET Ointment in children below 18 years have not been established.

Route of Administration
Topical use

Contraindications
a. Hypersensitivity to the active substances or to any of the excipients.
b. Due to the content of calcipotriol, CALCIBET Ointment is contraindicated in patients with known disorders of calcium metabolism.
c. Due to the content of corticosteroid, CALCIBET Ointment is contraindicated in the following conditions: viral (eg. Herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tubercu osis, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds.
d. Contraindicated in erythrodermia, exfoliative and pustular psoriasis.

Warnings & Precautions
Effects on endocrine system
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.
Effects on calcium metabolism
Due to the content of calcipotriol, hypercalcaemia may occur if the maximum daily dose (15g) is exceeded. Serum calcium is normalized when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommen dations relevant to calcipotriol are followed.
Treatment of more than 30% of the body surface should be avoided.
Local adverse reactions
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.
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.
Unevaluated uses
There is no experience with the use of calcipotriol/ betamethasone in guttate psoriasis.
Concurrent treatment and UV exposure
There is limited experience for the use of this medicinal product on the scalp. Calcipotriol/ betamethasone ointment for body psoriasis lesions has been used in combination with calcipotriol/ betamethasone gel for scalp psoriasis lesions but there is limited experience of combination of calcipotriol/ betamethasone 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.
Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient present 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.

Interactions with Other Medicaments
No interaction studies have been performed with calcipotriol / betamethasone.

Pregnancy and Lactation
1) Pregnancy
There are inadequate data from the use of calcibet ointment in pregnant women. Therefore, during pregnancy, calcibet ointment should only be used when the potential benefits justify the potential risks.
2) Lactation
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 Calcibet ointment to women who breast-feed. The patient should be instructed not to use calcipotriol/ betamethasone on the breast when breast feeding.

Side Effects
The most frequently reported adverse reactions during treatment are various skin reactions like pruritus and skin exfoliations. Pustular psoriasis and hypercalcaemia have also 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	Skin infection* Folliculitis
Rare	Furuncle
Immune system disorders	
Rare	Hypersensitivity
Metabolism and nutrition disorders	
Rare	Hypercalcaemia
Eye disorders	
Not known	Vision, blurred (see also section 4.4), chorioretinopathy
Skin and subcutaneous tissue disorders	
Common	Skin exfoliation Pruritus
Uncommon	Skin atrophy Exacerbation of psoriasis Dermatitis Erythema Rash** Purpura or ecchymosis Skin burning sensation Skin irritation
Rare	Pustular psoriasis Skin striae Photosensitivity reaction Acne Dry skin
General disorders and administration site conditions	
Uncommon	Application site pigmentation changes Application site pain***
Rare	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
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.
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.

Symptoms and Treatment of 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.

Effects on Ability to Drive and Use Machine
Calcipotriol/Betamethasone has no or negligible influence on the ability to drive and to use machines.

Preclinical Safety Data
Not applicable

Instructions for Use
CALCIBET 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 CALCIBET Ointment.

Storage Condition
Store below 30℃. For external use only. Keep out of reach of children.

Shelf Life
24 months from manufacturing date

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

Packing
30g/Aluminum tube/Box

MANUFACTURER
GENUONE Sciences Inc.
245 Sandangil, Jeoneui-myeon, Sejong-si, Republic of Korea

PRODUCT REGISTRATION HOLDER
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