PRODUCT MONOGRAPH

PrTARO-CALCIPOTRIOL / BETAMETHASONE GEL

calcipotriol and betamethasone dipropionate gel

50 mcg/g calcipotriol (as monohydrate)
and
0.5 mg/g betamethasone (as dipropionate)
gel

Topical Antipsoriatic Agent
Vitamin D Analogue / Corticosteroid

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calcipotriol and betamethasone dipropionate gel

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
topical	Gel; 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate)	Alpha-tocopherol, Butylated hydroxytoluene, Hydrogenated castor oil, Mineral oil, Polyoxypropylene stearyl ether

INDICATIONS AND CLINICAL USE

Taro-Calcipotriol / Betamethasone Gel (calcipotriol and betamethasone dipropionate gel) is indicated for the topical treatment of:

- Moderate to severe scalp psoriasis vulgaris in patients 18 years and older for up to 4 weeks.
- Mild to moderate plaque psoriasis vulgaris on the body in patients 18 years and older for up to 8 weeks

CONTRAINDICATIONS

- Known hypersensitivity to Taro-Calcipotriol / Betamethasone Gel, to any ingredient in the formulation or to components of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Ophthalmic use
- Patients with known disorders of calcium metabolism.
- Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis
- Perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers ,wounds, perianal and genital pruritus.
- Guttate, erythrodermic, exfoliative and pustular psoriasis.
- Patients with severe renal insufficiency or severe hepatic disorders.

WARNINGS AND PRECAUTIONS

General

Taro-Calcipotriol / Betamethasone Gel should not be used on the face, axillae, flexures, groin, or genitals. (see WARNINGS AND PRECAUTIONS/Skin).

Hypercalcemia, hypercalciuria and hypothalamic-pituitary-adrenal (HPA) axis suppression have been observed with the use of calcipotriol and betamethasone dipropionate gel. (see WARNINGS AND PRECAUTIONS/Endocrine and Metabolism).

Carcinogenesis and Mutagenesis

Calcipotriol when used in combination with ultraviolet radiation (UVR) may enhance the known skin carcinogenic effect of UVR. This potential risk is based on the pre-clinical finding in mice of a reduced time to tumor formation from long term exposure of UVR and topically applied calcipotriol (see TOXICOLOGY, Carcinogenicity).

Patients who apply Taro-Calcipotriol / Betamethasone Gel to exposed skin (e.g. a bald scalp) should avoid excessive exposure to both natural and artificial sunlight (e.g. phototherapy, tanning beds, sun lamps, etc.).

Endocrine and Metabolism

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

Application of topical corticosteroid products including Taro-Calcipotriol / Betamethasone Gel on large areas of broken skin (i.e. open sores), on mucous membranes, in skin folds or under occlusive dressings should therefore be avoided. The use of occlusion may increase penetration

of the drug into the stratum corneum, increasing the risk of adverse events.

Manifestations of Cushing's syndrome, effects on the metabolic control of diabetes mellitus (e.g. hyperglycaemia, glucosuria) and unmasking of latent diabetes mellitus can also be produced in some patients by systemic absorption of topical corticosteroids.

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression (see WARNINGS AND PRECAUTIONS/Monitoring and Laboratory Tests).

Hypercalcemia and hypercalciuria have been observed with the use of calcipotriol and betamethasone dipropionate gel. If hypercalemia or hypercalciuria develop, treatment should be discontinued until parameters of calcium metabolism have normalized. The effects of calcipotriol and betamethasone dipropionate gel on calcium metabolism following treatment durations of more than 8 weeks have not been evaluated. (see WARNINGS AND PRECAUTIONS/Monitoring and Laboratory).

Ophthalmologic

Taro-Calcipotriol / Betamethasone Gel is not for ophthalmic use. Taro-Calcipotriol / Betamethasone Gel may cause eye irritation. Avoid contact with the eyes or conjunctiva.

Skin

Taro-Calcipotriol / Betamethasone Gel contains a potent World Health Organization (WHO) group III steroid and concurrent treatment with other corticosteroids on the same treatment area must be avoided.

Taro-Calcipotriol / Betamethasone Gel should not be used on the face, axillae, flexures, groin, or genitals. The patient must be instructed in the correct use of Taro-Calcipotriol / Betamethasone Gel (e.g. washing their hands after each application) to avoid accidental transfer or application to these regions or to the mouth, mucous membranes or eyes (see DOSAGE AND ADMINISTRATION).

Facial skin is very sensitive to Vitamin D analogues and corticosteroids. Dermatitis has been observed with the use of calcipotriol and betamethasone dipropionate gel. Should facial dermatitis develop, treatment with Taro-Calcipotriol / Betamethasone Gel on the scalp should be discontinued.

With long-term use, there is an increased risk of local and systemic corticosteroid adverse reactions. Treatment should be discontinued in the case of corticosteroid adverse reactions related to long-term use of Taro-Calcipotriol / Betamethasone Gel. (see ADVERSE REACTIONS).

When treating psoriasis with topical corticosteroid containing products, including Taro-Calcipotriol / Betamethasone Gel, it is recommended that treatment be interrupted periodically. There may be a risk of generalised pustular psoriasis or rebound psoriasis when discontinuing corticosteroids. Medical supervision should therefore continue in the post-treatment period.

Concomitant skin infections should be treated with an appropriate antimicrobial agent. If the infection worsens, Taro-Calcipotriol / Betamethasone Gel should be discontinued until the infection has been adequately treated.

Special Populations

Pregnant Women: The safety of calcipotriol and/or topical corticosteroids for use during pregnancy has not been established. Pregnant women were excluded from the clinical studies conducted with calcipotriol and betamethasone dipropionate gel. When given systemically, calcipotriol has been shown to be fetotoxic and betamethasone dipropionate has been shown to be teratogenic in animals (see PART II, TOXICOLOGY, Reproduction and Mutagenicity). The use of Taro-Calcipotriol / Betamethasone Gel is not recommended in pregnant women.

Nursing Women: The safety of calcipotriol and/or topical corticosteroids for use in nursing women has not been established. It is not known whether calcipotriol can be excreted in breast milk. Betamethasone passes into breast milk, but it is not known if topical application of corticosteroid containing products, including Taro-Calcipotriol / Betamethasone Gel, can lead to sufficient systemic absorption to produce detectable quantities in breast milk.

Caution should be exercised when prescribing Taro-Calcipotriol / Betamethasone Gel to women who breastfeed. The patient should be instructed not to use Taro-Calcipotriol / Betamethasone

Gel on the breast when breastfeeding.

Pediatrics (<18 years of age): Since there is no clinical trial experience with the use of calcipotriol and betamethasone dipropionate gel in children, use of Taro-Calcipotriol / Betamethasone Gel is not recommended. Children may demonstrate greater susceptibility to systemic corticosteroid related adverse effects due to a larger skin surface area to body weight ratio as compared to adults.

Geriatrics (≥ 65 years of age): Of the 824 patients treated with calcipotriol and betamethasone dipropionate gel for psoriasis on the body in controlled Phase II and III clinical studies, 124 were at least 65 years of age, and 36 were at least 75 years of age. Blood parathyroid hormone increase was reported more frequently in subjects 65 years and older. The clinical significance of this is not known. Of the 1,953 patients treated with calcipotriol and betamethasone dipropionate gel for scalp psoriasis in the controlled clinical studies, 334 were 65 years or older, and 84 were 75 years or older. Overall the adverse event reporting rate for calcipotriol and betamethasone dipropionate gel was comparable between subjects aged 65 years of age and over and those younger than 65.

Monitoring and Laboratory Tests

Treatment with calcipotriol and betamethasone dipropionate gel in the recommended amounts (See DOSAGE AND ADMINISTRATION) does not generally result in changes in laboratory values. However, in patients at risk of hypercalcaemia it is recommended that baseline serum calcium levels be obtained before starting treatment with subsequent monitoring of serum calcium levels at suitable intervals. If serum calcium becomes elevated, Taro-Calcipotriol / Betamethasone Gel administration should be discontinued and serum calcium levels should be measured once weekly until they return to normal.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA Axis function is generally prompt and complete upon discontinuation of topical corticosteroids (see Endocrine and Metabolism / ACTION AND CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Overview

Studies on the Body

In a safety pool of randomized, multi-centre prospective vehicle- and/or active controlled clinical trials in subjects with plaque psoriasis on non-scalp areas, patients applied study product once daily for up to 8 weeks. A total of 824 patients were treated with calcipotriol and betamethasone dipropionate gel and the mean weekly dose was 29.0g (median 22.6g). Adverse drug reactions were adverse events that the investigators considered at least possibly related to study treatment. Approximately 6% of patients treated with calcipotriol and betamethasone dipropionate gel experienced an adverse reaction. In this safety pool, the most common adverse reaction in the calcipotriol and betamethasone dipropionate gel group was pruritus.

In the safety pool of controlled clinical trials, adverse reactions led to discontinuation of treatment with calcipotriol and betamethasone dipropionate gel in 0.8% of patients. Patients discontinued treatment due to the following adverse reactions: application site pain, pain of skin, skin irritation, dermatitis contact, dry skin, pruritus and psoriasis.

Studies on the Scalp

The clinical trial programme for calcipotriol and betamethasone dipropionate gel has included more than 1,900 patients with scalp psoriasis treated with calcipotriol and betamethasone dipropionate gel. Approximately 8% of patients treated with calcipotriol and betamethasone dipropionate gel experienced an adverse reaction. Based on data from clinical trials, the most common adverse reaction is pruritus.

Adverse reactions led to discontinuation of treatment with calcipotriol and betamethasone dipropionate gel in 0.1-0.2% of patients. Patients discontinued treatment due to the following adverse reactions: pruritus, skin pain or irritation, dermatitis, eye irritation, rash, burning sensation, face oedema, folliculitis and dry skin.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction

information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Studies on the Body

One randomized, double-blind, vehicle-controlled, 8-week pivotal trial (n=1152) was conducted to evaluate the efficacy and safety of calcipotriol and betamethasone dipropionate gel compared to betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle, calcipotriol 50 mcg/g in the gel vehicle and the gel vehicle-alone administered once daily in subjects with mild to moderate psoriasis vulgaris on non-scalp regions of the body (trunk and/or limbs). Mild to moderate psoriasis vulgaris was determined by the Investigator's global assessment of disease severity (IGA).The mean baseline extent of psoriasis was similar among the four treatment groups (approximately 11-13% of body surface area). The mean amount of study medication used per week over the course of the study was similar among the calcipotriol and betamethasone dipropionate gel, betamethasone gel and gel vehicle groups (approximately 28-32 g/week) and greatest in the calcipotriol group (approximately 37g/week).

Adverse drug reactions were adverse events that the investigators considered at least possibly related to study treatment. In the pivotal study, the incidence of withdrawal due to adverse reactions was highest in the calcipotriol gel group (5.2%) vs. 0.6% in the calcipotriol and betamethasone dipropionate gel group, 0% in the betamethasone gel group and 0% in the vehicle group. Among patients treated with calcipotriol and betamethasone dipropionate gel, the adverse drug reactions leading to withdrawal were: application site pain, psoriasis, and dermatitis contact. Signs of skin atrophy were assessed visually by the investigator. There were no reports in any treatment group that were related to skin atrophy, striae, telangiectasia, skin hypopigmentation or hypertrichosis.

Table 1 lists adverse drug reactions reported in at least 1% of subjects in any treatment group in the pivotal trial of calcipotriol and betamethasone dipropionate gel on the body. Overall, adverse drug reactions were reported most frequently in the calcipotriol gel group (5.3%), followed by the calcipotriol and betamethasone dipropionate gel group (5.0%), the vehicle group (4.2%) and the betamethasone gel group (3.1%).

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Patients for the Pivotal Body Study: safety analysis set

	Calcipotriol and Betamethasone dipropionate gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Gel vehicle (n=95)
Primary System Organ Class[1] Preferred Term[1]	**Number of Patients (%)**	**Number of Patients (%)**	**Number of Patients (%)**	**Number of Patients (%)**
Ear and labyrinth disorders				
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
General disorders and administration site disorders				
Application site pain	2 (0.4)	1 (0.2)	0 (0.0)	1 (1.1)
Infections and infestations				
Candidiasis	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations				
Blood parathyroid hormone increased	7 (1.5)	6 (1.3)	0 (0.0)	1 (1.1)
Skin and subcutaneous tissue disorders				
Dermatitis contact	1 (0.2)	0 (0.0)	1 (1.1)	0 (0.0)
Pruritus	3 (0.6)	0 (0.0)	1 (1.1)	2 (2.1)
Psoriasis	1 (0.2)	0 (0.0)	1 (1.1)	0 (0.0)
Rash papular	1 (0.2)	0 (0.0)	0 (0.0)	1 (1.1)
Skin irritation	0 (0.0)	1 (0.2)	1 (1.1)	0 (0.0)

[1] Coded according to MedDRA version 13.0

Clinical Studies on the Scalp

Two pivotal and 4 supporting controlled clinical studies were conducted in scalp psoriasis. For the pivotal scalp studies, adverse drug reactions reported by at least 1% of patients in any treatment group are summarized in Table 2. Overall, the incidence of patients with at least one ADR was lowest in the calcipotriol and betamethasone dipropionate gel group.

Table 2. Adverse Drug Reactions Occurring in ≥ 1% of Patients for the Pivotal Scalp Studies: safety analysis set

	Calcipotriol and Betamethasone dipropionate. gel (n=1093)	Betamethasone gel (n=1104)	Calcipotriol gel (n=548)	Gel vehicle (n=135)
Primary System Organ Class[1] Preferred Term[1]	**Number of Patients (%)**	**Number of Patients (%)**	**Number of Patients (%)**	**Number of Patients (%)**
Nervous system disorders				
Headache	6 (0.5)	11 (1.0)	1 (0.2)	1 (0.7)
Burning sensation	2 (0.2)	6 (0.5)	10 (1.8)	0 (0.0)
Skin and subcutaneous tissue disorders				
Pruritus	25 (2.3)	18 (1.6)	45 (8.2)	7 (5.2)
Skin irritation	5 (0.5)	5 (0.5)	15 (2.7)	3 (2.2)
Alopecia	4 (0.4)	6 (0.5)	3 (0.5)	2 (1.5)
Erythema	4 (0.4)	4 (0.4)	16 (2.9)	1 (0.7)
Dry skin	1 (0.1)	3 (0.3)	6 (1.1)	0 (0.0)
General disorders and administration site conditions				
Pain	1 (0.1)	0 (0.0)	3 (0.5)	3 (2.2)

[1] Coded according to MedDRA version 6.1.

Less Common Clinical Trial Adverse Drug Reactions (<1%) for Studies on the Body

The following is a list of less common adverse reactions reported in the pivotal trial conducted in body psoriasis. Adverse reactions reported in <1% of patients treated with calcipotriol and betamethasone dipropionate gel and not otherwise listed in Table 1 above, are included. Adverse reactions are listed by MedDRA SOC.

General Disorders and Administration Site Conditions: Application site pain, feeling of body temperature change.

Infections and Infestations: Cellulitis, folliculitis and sinusitis.

Investigations: Blood phosphorus decreased.

Nervous System Disorder: Dizziness

Skin and Subcutaneous Tissue Disorders: Dermatitis, guttate psoriasis, rash

Vascular Disorders: Flushing

Less Common Clinical Trial Adverse Drug Reactions (<1%) for Studies on the Scalp

From clinical trials conducted in scalp psoriasis, the uncommon adverse reactions are listed by MedDRA SOC from most to least frequent.

Eye Disorders: eye irritation.

Infections: otitis externa.

Investigations: elevated blood calcium.

Skin and Subcutaneous Tissue Disorders: burning sensation of the skin, skin pain or irritation, folliculitis, dermatitis, contact dermatitis, erythema, acne, dry skin, exacerbations of psoriasis, rash and pustular rash, and face oedema.

See also ACTION AND CLINICAL PHARMACOLOGY and Part II: CLINICAL TRIALS, Special Studies.

Other Adverse Drug Reactions

Adverse reactions observed for the individual drug substances calcipotriol and betamethasone dipropionate are described below.

Calcipotriol

Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, aggravated psoriasis, photosensitivity and hypersensitivity reactions. There have been very rare cases of angioedema and facial oedema. Very rare cases of hypercalcaemia or hypercalciuria have been reported (see WARNINGS AND PRECAUTIONS).

Betamethasone 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 corticosteroid containing products, including calcipotriol and betamethasone dipropionate gel in adults occur infrequently but 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. Application of Taro-Calcipotriol / Betamethasone Gel under occlusion, on large areas or for prolonged treatment periods may result in an increased risk of systemic adverse events, and is therefore not

recommended (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

The following serious and unexpected adverse events not previously listed in the clinical trial adverse reactions section of the Product Monograph have been reported. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The list below includes reactions reported in patients using the gel and/or ointment formulations of calcipotriol and betamethasone dipropionate.

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: auricular swelling

Eye disorders: glaucoma

General disorders and administration site conditions: drug ineffective, oedema peripheral

Infections and infestations: gastroenteritis, respiratory tract infection, staphylococcal infection, upper respiratory tract infection

Injury, poisoning and procedural complications: overdose

Nervous system disorders: migraine, tension headache

Psychiatric disorders: suicidal ideation

Renal and urinary disorders: nephrolithiasis

Respiratory, thoracic and mediastinal disorders: dyspnoea

Skin and subcutaneous tissue disorders: erythrodermic psoriasis, skin atrophy, skin exfoliation

Surgical and medical procedures: off label use

Vascular disorders: haematoma

DRUG INTERACTIONS

Drug-Drug Interactions

No drug interaction studies have been performed with calcipotriol and betamethasone dipropionate.

Drug-Lifestyle Interactions

Patients who apply Taro-Calcipotriol / Betamethasone Gel to exposed skin (e.g. a bald scalp) should avoid excessive exposure to both natural and artificial sunlight (e.g. phototherapy, tanning

beds, sun lamps, etc.). (See WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Taro-Calcipotriol / Betamethasone is available in a bottle format.

Recommended Dose and Dosage Adjustment

Taro-Calcipotriol / Betamethasone Gel should be applied to affected areas of the body once daily for up to 8 weeks and to affected areas of the scalp once daily for up to 4 weeks. After satisfactory improvement has occurred, the drug can be discontinued. If recurrence takes place after discontinuation, treatment may be reinstituted.

The maximum daily dose should not exceed 15 g and the maximum weekly dose should not exceed 100 g of Taro-Calcipotriol / Betamethasone Gel and/or other products containing calcipotriol. The total body surface area treated, including scalp and body should not exceed 30%.

Taro-Calcipotriol / Betamethasone Gel is not recommended for use in children and adolescents below the age of 18 years.

Missed Dose

If a dose is missed, the patient should apply Taro-Calcipotriol / Betamethasone Gel when he/she remembers, but only once on a given day and then continue on as usual.

Administration

Application under occlusive dressings should be avoided since it increases systemic absorption of corticosteroids.

Taro-Calcipotriol / Betamethasone Gel should not be applied directly to the face, eyes, flexures, groin or genitals (see WARNINGS AND PRECAUTIONS/Ophthalmologic, and WARNINGS AND PRECAUTIONS/Skin).

The bottle should be **shaken** before each use and Taro-Calcipotriol / Betamethasone Gel applied to the affected area. The hands should be washed after use.

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 Taro-Calcipotriol / Betamethasone Gel. Taro-Calcipotriol / Betamethasone Gel should remain on the skin during the night or during the day. Patients should be advised that Taro-Calcipotriol / Betamethasone Gel should not be applied to the scalp 12 hours before or after colouring, perming or any chemical hair treatments.

OVERDOSAGE

Use of Taro-Calcipotriol / Betamethasone Gel (calcipotriol and betamethasone dipropionate gel) above the recommended dose may cause elevated serum calcium which should subside when treatment is discontinued. In such cases, it is recommended to monitor serum calcium levels once weekly until they return to normal. The symptoms of hypercalcemia include polyuria, constipation, muscle weakness, confusion and coma.

Excessive prolonged use of topical corticosteroid containing products, including Taro-Calcipotriol / Betamethasone Gel, may suppress the pituitary-adrenal functions, resulting in secondary adrenal insufficiency which is usually reversible. If this occurs, symptomatic treatment is indicated. In cases of chronic toxicity, treatment with Taro-Calcipotriol / Betamethasone Gel must be discontinued gradually.

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Taro-Calcipotriol / Betamethasone Gel is a combination of the vitamin D analogue calcipotriol and the corticosteroid betamethasone dipropionate.

Calcipotriol is a non-steroidal antipsoriatic agent, derived from the naturally occurring

vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the 1,25 (OH)2D3 receptor. Calcipotriol is as potent as 1,25(OH)2D3, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than 1,25(OH)2D3 in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation of keratinocytes (without any evidence of a cytotoxic effect), thus reversing the abnormal keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Topical corticosteroids such as betamethasone dipropionate have anti-inflammatory, anti-pruritic, vasoconstrictive and immunosuppressive properties. In general, the mechanism of the anti-inflammatory activity of topical corticosteroids is unclear. Corticosteriods are thought to induce phospholipase A_2 inhibitor proteins, preventing arachidonic acid release and the biosynthesis of potent mediators of inflammation.

Pharmacodynamics

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 dipropionate gel (on the scalp) and calcipotriol and betamethasone dipropionate ointment (on the body) (study A). 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.

In addition, HPA axis suppression was evaluated in adult patients (n=43) with extensive psoriasis involving 15-30% of the body surface area (including the scalp) (study B). Treatment consisted of once daily application of calcipotriol and betamethasone dipropionate gel on the body and the scalp for up to 8 weeks. Adrenal suppression, as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL, was observed in 3 of 43 patients (7%) after 4 weeks of treatment and in 0 of the 36 patients who provided data after 8 weeks treatment.

A study was conducted to evaluate the atrophogenic potential of betamethasone dipropionate in

calcipotriol and betamethasone dipropionate gel compared with marketed betamethasone dipropionate ointment and gel vehicle. The study was conducted as an intra-individual comparison of once daily application for 4 weeks in 48 healthy volunteers. Skin thickness was measured by sonography performed before treatment, weekly during the 4-week treatment period and 2 weeks after the end of treatment. Calcipotriol and betamethasone dipropionate gel induced reversible skin thinning, which was similar to that induced by betamethasone dipropionate ointment.

Pharmacokinetics

Absorption: The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied calcipotriol and betamethasone dipropionate gel is comparable to calcipotriol and betamethasone dipropionate ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone dipropionate from the calcipotriol and betamethasone dipropionate ointment formulation 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.

Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients with extensive psoriasis involving the scalp and body and treated for 4 or 8 weeks with calcipotriol and betamethasone dipropionate gel on the scalp and calcipotriol and betamethasone dipropionate ointment on the body. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients. While the biological activity of the calcipotriol metabolite is less than that of calcipotriol, the activity of the betamethasone dipropionate metabolite cannot be distinguished from the activity of the parent compound.

The serum levels of calcipotriol and betamethasone dipropionate and their major metabolites were measured after 4 weeks of once daily application of calcipotriol and betamethasone dipropionate gel to 15-30% of the body surface area (body and scalp areas). Calcipotriol and its major metabolite were below the lower limit of quantification in all serum samples and betamethasone dipropionate was quantifiable in 1 of the samples in 5 of 43 (11.6%) patients. The primary metabolite of betamethasone dipropionate was quantifiable in 16 of 43 (37.2%) patients.

Metabolism: Calcipotriol metabolism following systemic uptake is rapid and occurs in the liver. Calcipotriol is metabolized to MC1046 (the α,β-unsaturated ketone analog of calcipotriol), which is metabolized further to MC1080 (a saturated ketone analog). MC1080 is the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate is metabolized to betamethasone 17-propionate and betamethasone, including the 6β-hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.

STORAGE AND STABILITY

Store at 15° C to 30° C. Do not refrigerate. Keep out of reach of children and pets.
Protect from light, keep the bottle in the carton. Use within 6 months of first opening the bottle and before the expiry date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

Gel: almost clear, colourless to slightly off-white lipophilic gel.

Composition

50 mcg/g calcipotriol (as monohydrate) plus 0.5 mg/g betamethasone (as dipropionate)

Non-medicinal ingredients: alpha-tocopherol, butylated hydroxytoluene, hydrogenated castor oil, mineral oil and polyoxypropylene stearyl ether.

Packaging

Available in cartons of 1 or 2 polyethylene bottles of 60 g.

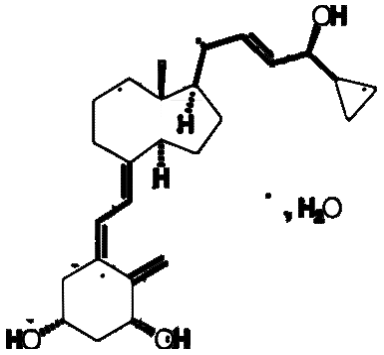
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

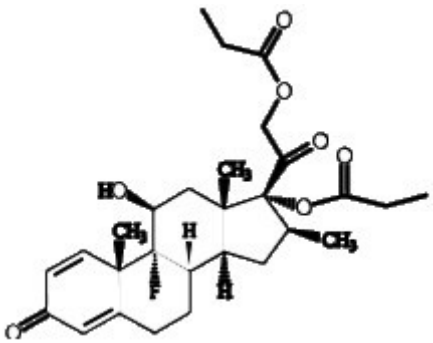
Drug Substance

Proper name (I.N.N.):	Calcipotriol monohydrate	Betamethasone dipropionate
Chemical name:	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclopropyl-, monohydrate, (1α,3β,5Z,7E,22E,24S)	Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-(11β,16β)
Alternative chemical name:	20(R)-(3'(S)-Cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-1(S),3(R)-dihydroxy-9-10-secopregna-5(Z),7(E),10(19)-triene, hydrate	9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate
Molecular formula:	$C_{27}H_{40}O_3$, H_2O	$C_{28}H_{37}FO_7$
Molecular mass:	430.6 g/mol	504.6 g/mol
Chirality:	The calcipotriol molecule is one single stereoisomer. The absolute configuration of the chiral centres at carbon atoms nos. 1, 3, 13, 14, 17, 20 and 24 is indicated in the structural formula below.	

Structural formula:
Calcipotriol monohydrate



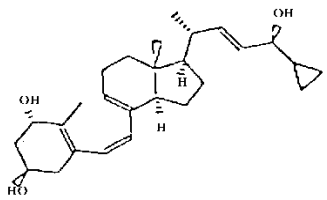
Betamethasone dipropionate



Physicochemical properties :

	Calcipotriol monohydrate	Betamethasone dipropionate
Physical form:	White or almost white crystalline substance.	White or almost white crystalline powder.
Solubility at room temperature:	Freely soluble in ethanol, soluble in chloroform and propylene glycol, practically insoluble in liquid paraffin. Solubility in water is 0.6 mcg/ml.	Freely soluble in acetone, in dioxane, in dichloromethane and in chloroform; soluble in methanol; sparingly soluble in alcohol; slightly soluble in ether; insoluble in water and in hexane.
Melting point:	166-168 °C	176-180 °C
Polymorphism:	So far no signs have indicated the existence of polymorphic forms.	

Other characteristics: Calcipotriol is a vitamin D derivative. It is well-known that vitamin D in solution forms a reversible temperature dependent equilibrium between vitamin D and pre-vitamin D (described in (i.e.) J Pharm Sci 1968; 57:1326). In the same way, solutions of calcipotriol establish an equilibrium with "pre-calcipotriol". The structural formula of "pre-calcipotriol" is shown below.



CLINICAL TRIALS

Comparative Studies

A single-center, randomized, single-exposure, open-label study conducted on healthy male and non-pregnant female subjects compared the vasoconstriction response of a 10 µL aliquot of Taro-Calcipotriol / Betamethasone Gel (Taro Pharmaceuticals Inc.) to Dovobet® gel (50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate)). The study assessed vasoconstriction (blanching) using a chromameter. Results from the vasoconstrictor assay indicated *in vivo* equivalence between Taro-Calcipotriol / Betamethasone Gel and Dovobet® gel (see table below).

Study Primary Data Means of Negative $AUEC_{(0-24\ hour)}$ and 90% Confidence Interval

Parameter	*Number of Subjects*	*$AUEC_{(0-24hr)}$*		*T/R Ratio[a]*	*90% CI[b]*	
		Test	*Reference*		*Low*	*High*
$AUEC_{0-24}$	60	-17.0	-16.6	102.4	95.6	109.7

AUEC = area under the effect curve; $AUEC_{(0-24hr)}$ = area under the effect curve from 0 to 24 hr;
CI = confidence interval; R = Reference (Dovobet® from Leo Pharma Inc, Canada);
T = Test (Taro-Calcipotriol / Betamethasone).

a. Ratio calculated as Test mean divided by the Reference mean, expressed as a percentage.
b. Confidence interval on the ratio expressed as a percentage, calculated using Locke's Method

A multi-center, double-blind, randomized, placebo-controlled, parallel-group study was conducted, comparing Taro-Calcipotriol / Betamethasone Gel (Taro Pharmaceuticals Inc.) to Dovobet® gel (50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate)) (Leo Pharma Inc., Canada), and both active treatments to a placebo control in treatment of body psoriasis in 467 subjects with mild to moderate body plaque psoriasis vulgaris. The study drug was applied topically once daily to provide a sufficient amount on affected area(s) of the body to cover plaque with an even layer, for a total treatment duration of 56 days. Bioequivalence between Taro-Calcipotriol / Betamethasone Gel and Dovobet® gel was established for the primary endpoint of "controlled disease" at week 8 (see table below).

Primary Endpoint: "Controlled Disease" at Week 8		
Parameter	**Test**	**Reference**
n (**Per protocol Population**)	127	125
"Controlled Disease" percent	34.6	30.4
Percent difference	4.2	
90% CI	(-6.2, 14.7)	

Clinical Studies on the Body

One randomized, double-blind, vehicle-controlled, 8-week pivotal trial (n=1152) was conducted to evaluate the efficacy and safety of calcipotriol and betamethasone dipropionate gel compared to betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle, calcipotriol 50 mcg/g in the gel vehicle and the gel vehicle-alone administered once daily in patients with mild to moderate psoriasis vulgaris on non-scalp regions of the body (trunk and/or limbs, including neck, hands, buttocks and feet). The scalp, face, flexures and genitals were not treated and were not assessed as part of the efficacy analysis. Patients had mild to moderate psoriasis vulgaris at baseline, as determined by the Investigator's Global Assessment of disease severity (IGA). Patients were also to have a minimum modified Psoriasis Area and Severity Index (PASI) score for extent of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms and/or 10% of trunk, and/or 10% of legs).

Seventy-eight (78%) percent of patients had disease of moderate severity at baseline. The mean baseline extend of psoriasis was similar among the four treatment groups (approximately 11-13% of body surface area). The average amount of study medication used per week over the course of the study was similar among the calcipotriol and betamethasone dipropionate gel, betamethasone gel and gel vehicle groups (approximately 28-32 g/week) and greatest in the calcipotriol group (approximately 37g/week). The mean age was 48.6 years (range 18-88 years) and approximately 60% of patients were male. The majority of patients were White (89.1%), 6.2% were Black or African American and 2.6% were Asian.

Results for the co-primary response criterion [percentage of patients who achieved "controlled disease" according to the IGA at weeks 4 and 8] showed that calcipotriol and betamethasone dipropionate gel was statistically significantly more effective than each of the individual components alone at Week 8. At Week 4, although statistical significance was not achieved for the comparison with betamethasone in gel vehicle, calcipotriol and betamethasone dipropionate gel was statistically significantly more effective than calcipotriol in gel vehicle (see table below).

% of Patients with controlled disease (clear or almost clear)*	Calcipotriol and Betamethasone dipropionate gel (n = 482)	Betamethasone Dipropionate in gel vehicle (n = 479)	Calcipotriol in gel vehicle (n = 96)	Gel vehicle (n=95)
week 4	13.3%	12.5%	5.2%†	2.1%†
week 8	29.0%	21.5%§	14.6%§	6.3%§

* Patients with mild disease at baseline were required to be "Clear" to be considered controlled. Patients with moderate disease at baseline were required to be "Clear" or "Almost clear".

† calcipotriol and betamethasone dipropionate gel statistically significantly more effective than comparator treatment gel ($p<0.05$)

§ calcipotriol and betamethasone dipropionate gel statistically significantly more effective than comparator treatment gel ($p<0.01$)

Clinical Studies on the Scalp

The efficacy of once daily use of calcipotriol and betamethasone dipropionate gel was investigated in two randomised, double- blind 8-week clinical studies including a total of more than 1,000 calcipotriol and betamethasone dipropionate gel treated patients with scalp psoriasis of at least moderate severity according to the IGA. The number of patients with mild scalp psoriasis included in the studies was small making estimates of efficacy less reliable in this subgroup. 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 and betamethasone dipropionate gel was statistically significantly more effective than the comparators (see table below). The majority of patients who responded achieved satisfactory improvement before 4 weeks of treatment. Further increases in efficacy beyond 4 weeks were minimal. Results for speed of onset based on data at week 2 also showed calcipotriol and betamethasone dipropionate gel to be statistically significantly more effective than the comparators.

% of Patients with absent or very mild disease	Calcipotriol and Betamethasone dipropionate gel (n=1,108)*	Betamethasone dipropionate (n=1,118)*	Calcipotriol (n=558)*	Gel vehicle (n=136)*
week 2	53.2%	42.8%†	17.2%†	11.8%†
week 4	60.7%	52.9%†	24.7%†	14.7%†
week 8	69.8%	62.5%†	40.1%†	22.8%†

† calcipotriol and betamethasone dipropionate gel statistically significantly more effective than comparator treatment gel ($p<0.001$)

* including patients graded as mild at baseline

Another randomised, investigator-blinded clinical study including 312 patients with scalp psoriasis of at least moderate severity according to the IGA, investigated use of calcipotriol and betamethasone dipropionate gel once daily compared with calcipotriol 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 and betamethasone dipropionate gel was statistically significantly more effective than calcipotriol scalp solution (see table below).

% of Patients with absent or very mild disease	Calcipotriol and Betamethasone dipropionate gel (n=207)	Calcipotriol scalp solution (n=105)
week 4	55.1%†	18.1%
week 8	68.6%†	31.4%

† statistically significantly more effective than calcipotriol scalp solution ($p<0.001$)

Special Studies

A randomised, double-blind, study of 873 patients with scalp psoriasis of at least moderate severity (according to the IGA), investigated the use of calcipotriol and betamethasone dipropionate gel compared with calcipotriol in the gel vehicle. Both treatments were applied once daily, intermittently as required, for up to 52 weeks. The average amount of study drug used was 10.6 g/week. Adverse events possibly related to prolonged use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference between the treatment groups (2.6% in the calcipotriol and betamethasone dipropionate gel group and 3.0% in the calcipotriol group; $p<0.73$) in the percentages of patients experiencing such adverse events. No cases of skin atrophy (based on a dermatologist's visual assessment) were reported.

Effects on adrenal function and calcium metabolism were investigated in an open-label study in 35 patients with extensive psoriasis on both scalp (at least 30% of scalp area) and body (15-30% of body surface area). Patients used an average of 23.7 g/week calcipotriol and betamethasone dipropionate gel on the scalp and an average of 40.2 g/week calcipotriol and betamethasone dipropionate ointment on the body. Adrenal response to ACTH was determined by measuring serum cortisol levels 30 and 60 minutes after ACTH challenge. A borderline decrease in cortisol response at 30 minutes post ACTH challenge

was seen in 5 of the 32 evaluable 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 a change in calcium metabolism observed in these patients.

Effects on adrenal function and calcium metabolism were also investigated using only calcipotriol and betamethasone dipropionate gel in an open-label study in 43 adult patients with extensive psoriasis involving 15-30% of the body surface area (including the scalp). Treatment consisted of once daily application of calcipotriol and betamethasone dipropionate gel on the body and the scalp for up to 8 weeks. Adrenal response to ACTH was determined by measuring serum cortisol levels 30 and 60 minutes after ACTH challenge. The mean baseline extent of psoriasis was 20.6% of body surface area. The mean amount of study drug used over the total treatment period was 52.3 g/week (range 7.6 g/week to 92.9 g/week).

Three (7.0%) subjects had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at week 4. None of the 36 subjects who continued to week 8 and had samples with data had a 30 minute serum cortisol ≤18 mcg/dL. The adrenal suppression was considered borderline in two of these subjects because the 30 minute value was only slightly below the defined cut off level and the 60 minute value showed adequate response. One subject showed clear signs of adrenal suppression with a cortisol level lower than the cut off level at both 30 and 60 minutes. There were no clinically relevant changes in mean serum or urinary calcium levels. Elevated urinary calcium levels outside the normal range were observed in 2 patients (1 at 4 weeks and 1 at 8 weeks).

SUMMARY OF CLINICAL TRIALS

Clinical Studies on the Body

STUDY CODE	STUDY TYPE / DURATION	STUDY DESIGN	DOSAGE/ ROUTE	TREATMENT / PATIENT NO.	RESULTS
LEO80185-G23	Efficacy, safety study in patients with psoriasis vulgaris on the body 8 weeks	Multi-centre, prospective, randomised, double-blind, active- and vehicle-controlled, parallel group study <u>Primary endpoint:</u> % of patients with controlled disease at weeks 4 and 8	1. Calcipotriol and Betamethasone dipropionate gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate) 2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate) 3. Calcipotriol in the gel vehicle (50 mcg/g) 4. Gel vehicle Once daily, topical	Calcipotriol and Betamethasone dipropionate gel, n=482; Betamethasone, n=479; Calcipotriol, n=96; Gel vehicle, n=95 Total 1152 randomized	There was no significant difference between calcipotriol and betamethasone dipropionate gel and betamethasone in gel vehicle in the percentage of patients who achieved controlled disease at week 4. Calcipotriol and betamethasone dipropionate gel (29%) was statistically significantly more effective than betamethasone in the gel vehicle (21.5%, p=0.008), calcipotriol in the gel vehicle (14.6%, p=.0.002 and the gel vehicle (6.3%, p<0.001) at achieving controlled disease at week 8. Adverse Events (AEs) were reported for 26.0% patients treated with calcipotriol and betamethasone dipropionate gel vs. 20.0% betamethasone in gel vehicle, 23.2% calcipotriol in gel vehicle and 23.2% gel vehicle. AEs in the treatment area occurred in 2.7% of patients in the calcipotriol and betamethasone dipropionate gel group vs. 2.3% in the betamethasone gel group, 4.2% in the calcipotriol gel group and 4.2% in the gel vehicle group.

SUMMARY OF CLINICAL TRIALS (*continued*)

Clinical Studies on the Scalp

STUDY CODE	STUDY TYPE / DURATION	STUDY DESIGN	DOSAGE/ ROUTE	TREATMENT / PATIENT NO.	RESULTS
MBL 0405 INT	Efficacy, safety study in patients with scalp psoriasis 8 weeks	Multi-centre, randomised, double-blind, active- and vehicle-controlled, parallel group study <u>Primary endpoint:</u> % of patients with controlled disease at week 8	1. Calcipotriol and Betamethasone dipropionate gel (50 mcg/g calcipotriol, as monohydrate + 0.5 mg/g betamethasone, as dipropionate) 2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate) 3. Calcipotriol in the gel vehicle (50 mcg/g) 4. Gel vehicle Once daily; topical	Calcipotriol and Betamethasone dipropionate gel, n=541; Betamethasone, n=556; Calcipotriol, n=272; Gel vehicle, n=136 Total 1505 randomized	Calcipotriol and betamethasone dipropionate gel (71.2%) was statistically significantly more effective than betamethasone in the gel vehicle (64.0%, p=0.011), calcipotriol in the gel vehicle (36.8%, p<0.001 and the gel vehicle (22.8%, p<0.001) at achieving controlled disease at wk 8. AEs for calcipotriol and betamethasone dipropionate gel and betamethasone in the gel vehicle were similar and favourable (34.5% vs.34.9%, respectively) compared with calcipotriol in the gel vehicle (46.2%) and the gel vehicle (40%). Lesional/perilesional AEs occurred in: 4.7% calcipotriol and betamethasone dipropionate gel, 5.3% betamethasone in the gel vehicle versus 13.2% calcipotriol in the gel vehicle and 13.3% the gel vehicle. Calcipotriol and betamethasone dipropionate gel was more effective in treating scalp psoriasis and the incidence of lesional/perilesional AEs was low.

SUMMARY OF CLINICAL TRIALS (*continued*)

Clinical Studies on the Scalp (continued))

STUDY CODE	STUDY TYPE / DURATION	STUDY DESIGN	DOSAGE/ ROUTE	TREATMENT / PATIENT NO.	RESULTS
MBL 0406 INT	Efficacy, safety study in patients with scalp psoriasis 8 weeks	Multi-centre, randomised, double-blind, active- controlled, parallel group study Primary endpoint: % of patients with controlled disease at week 8	1. Calcipotriol and Betamethasone dipropionate gel 2. Betamethasone in the gel vehicle (0.5 mg/g, as dipropionate) 3. Calcipotriol in the gel vehicle (50 mcg/g) Once daily; topical	Calcipotriol and Betamethasone dipropionate gel, n=568; Betamethasone, n=563; Calcipotriol, n=286 Total 1417 randomized	Calcipotriol and betamethasone dipropionate gel (68.4%) was statistically significantly more effective than betamethasone in the gel vehicle (61.0%, p=0.008) and calcipotriol in the gel vehicle (43.4%, p<0.001) at achieving controlled disease at wk 8. AEs for calcipotriol and betamethasone dipropionate gel and betamethasone in the gel vehicle were similar and favourable (38.7% vs. 41.0%, respectively) compared with calcipotriol in the gel vehicle (46.1%). Lesional/perilesional AEs occurred in: 6.2% calcipotriol and betamethasone dipropionate gel and 5.8% betamethasone in the gel vehicle versus 12.8% calcipotriol in the gel vehicle. Calcipotriol and betamethasone dipropionate gel was more effective in treating scalp psoriasis and the incidence of lesional/perilesional AEs was low.
MBL 0503 INT	Efficacy, safety, relapse and rebound study in patients with scalp psoriasis 8 weeks treatment + 8 weeks observation period (treatment–free)	Multi-centre, randomised, investigator-blinded, active-controlled, parallel group study Primary endpoint: % of patients with controlled disease at week 8	1. Calcipotriol and Betamethasone dipropionate gel (50 mcg/g calcipotriol , as monohydrate + 0.5 mg/g betamethasone, as dipropionate) Once daily; topical 2. Calcipotriol scalp solution (50 mcg/g calcipotriol) Twice daily; topical	Calcipotriol and Betamethasone dipropionate gel, n=207; Calcipotriol scalp solution, n=105 Total 312 randomized	Calcipotriol and betamethasone dipropionate gel (68.6%) was statistically significantly more effective than calcipotriol scalp solution (31.4%, p<0.001) at achieving controlled disease at wk 8. QoL measures favoured calcipotriol and betamethasone dipropionate gel. Frequency of AEs in the calcipotriol and betamethasone dipropionate gel group (34.5%) were significantly lower (p<0.001) than in the calcipotriol scalp solution group (56.7%). Lesional/perilesional AEs in the calcipotriol and betamethasone dipropionate gel group (3.4%) were significantly lower (p<0.001) than in the calcipotriol scalp solution group (19.2%). Calcipotriol and betamethasone dipropionate gel was more effective than calcipotriol scalp solution in treating scalp psoriasis.

DETAILED PHARMACOLOGY

Preclinical Pharmacology

Animal Pharmacodynamic Studies with Calcipotriol: The pharmacodynamic studies performed with calcipotriol have been aimed at establishing the activity of the compound as a regulator of cell differentiation and proliferation in cells possessing the receptor for the active form of vitamin D_3, $1,25(OH)_2D_3$. These studies are relevant for the intended clinical use in patients with psoriasis, due to the characteristic findings of epidermal hyperproliferation and incomplete keratinocyte differentiation in this disease.

Other current therapeutic agents act mainly through non-specific cytostatic/cytotoxic effects on the proliferating cells or suppression of underlying inflammatory and immunological reactions. In contrast, calcipotriol was shown to induce differentiation of low-differentiated human histiocytic lymphoma cells, of skin cells from newborn mice and of human keratinocytes. At the same time, proliferation was inhibited without evidence of any cytotoxic effect. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Calcipotriol was also found to inhibit cell proliferation induced by interleukin-1 but not by other related cellular mediators. Interleukin-1 is produced both by keratinocytes in the epidermis and by activated macrophages in the dermis. It is thought to play a pathogenetic role in psoriasis by activating both keratinocytes and immunological cells. Inhibition of interleukin-1 mediated effects in psoriatic skin by calcipotriol may therefore provide a way of regulating epidermal/dermal interactions in affected skin areas.

The pharmacodynamic studies performed *in-vitro* have shown that the activity of calcipotriol is very similar, both qualitatively and quantitatively, to that of $1,25(OH)_2D_3$. This is not surprising given the structural analogy of the two compounds and the ability of calcipotriol to bind to the cellular $1,25(OH)_2D_3$ receptor with the same affinity as $1,25(OH)_2D_3$ itself. *In-vivo* however, the effects of calcipotriol were significantly different from those of $1,25(OH)_2D_3$. The active form of vitamin D_3, $1,25(OH)_2D_3$, had potent effects on calcium metabolism and overdosage resulted in hypercalcemia and hypercalciuria.

From studies performed in rats, it was shown that the effect of calcipotriol on calcium metabolism was at least 100 to 200 times lower than that of $1,25(OH)_2D_3$. This low activity on calcium metabolism might be an intrinsic property of the calcipotriol molecule. However, the pharmacokinetic studies performed with calcipotriol suggested that the low activity on calcium metabolism was associated with a rapid metabolic degradation of the active compound.

Animal Pharmacokinetic Studies with Calcipotriol: Pharmacokinetic studies with ^{3}H-calcipotriol have been performed in rats and minipigs.

In vivo: Oral absorption of calcipotriol was approximately 60% in rats and 40% in minipigs. The half-life of calcipotriol was 12 minutes in rats and 60 minutes in minipigs. The major metabolite of calcipotriol MC1080 was present in the first plasma sample at 5 minutes; its half-life was 54 minutes in rats and 1.8 hours in minipigs. Drug-related radioactivity was excreted in urine and faeces and clearance was considered to be almost exclusively metabolic, as less than 5% of the administered radioactivity was excreted at the time of disappearance of all calcipotriol from plasma. Determination of the tissue distribution of calcipotriol was complicated by the appearance of ^{3}H-H_20 from the metabolic degradation of ^{3}H-calcipotriol. Autoradiography studies performed in rats, however, established that calcipotriol concentrations were highest in the liver, kidney and intestine. No drug-related radioactivity was present 24 hours after administration of ^{3}H-calcipotriol.

In vitro: Two main metabolites of calcipotriol were observed in incubations of calcipotriol with rat liver homogenate supernatants. The two metabolites, MC1046 and MC1080, were isolated, identified and synthesized. Both metabolites were also present in supernatants from minipig, rabbit and human liver homogenates and in plasma samples from rats and minipigs. Although the necessity of using very high dosages of calcipotriol precludes the study of calcipotriol metabolism in humans, the present evidence strongly suggests that calcipotriol metabolism is qualitatively similar in rats, minipigs, rabbits and humans. In addition, both metabolites had lost most of the biological activity associated with calcipotriol thus constituting a deactivation pathway for the drug.

Animal Pharmacokinetic Studies with Calcipotriol and Betamethasone: Studies were conducted in rats and minipigs to determine the extent of absorption and excretion of [^{3}H]-calcipotriol plus betamethasone and [^{3}H]-betamethasone plus calcipotriol after single dermal administration of the drug combination in gel and ointment formulations. In minipigs, absorption of calcipotriol and betamethasone dipropionate from the gel and ointment formulations was similar. In the rat, calcipotriol from the gel was significantly less absorbed than calcipotriol from the ointment. The main route of excretion for the gel and ointment was via the faeces for both calcipotriol and betamethasone.

IN VIVO PHARMACOKINETIC STUDIES WITH CALCIPOTRIOL AND BETAMETHASONE

TYPE OF STUDY	STUDY DESIGN	MAJOR RESULTS
Absorption and Excretion study in albino SD rats	Single dose of calcipotriol and betamethasone in a gel formulation compared an ointment formulation 6M, 6F rats per dose group (fed) Dermal application to 10cm^2 patch on the back 1) [^{3}H]-calcipotriol (50 µg/g) + betamethasone (500 µg/g) 2) Calcipotriol (50 µg/g) + [^{3}H]-betamethasone (500 µg/g) Sampling at 0, 6, 24, 48, 72, 96, 120, 144, 168 h Cumulative excretion of total (% of dose applied) radioactivity in urine, faeces, liver, serum, whole blood, dosed skin, carcass, cage wash	1) *Transdermal absorption of calcipotriol:* gel 10% (M9.0%, F11.6%), ointment 19% (male 15.8%, female 21.3%) Highest level found in faeces (gel, ointment), dosed skin (gel, ointment), and carcass (gel, ointment) 2) *Transdermal absorption of betamethasone: gel 8%* (M8.1%, F7.7%), ointment 9% (M9.3%, F8.9%) Highest level found in faeces (gel, ointment) and urine (gel, ointment) Absorption of betamethasone from the gel and ointment was similar. However, absorption of calcipotriol from the gel was significantly less than from the ointment. The main route of excretion was via the faeces for both calcipotriol and betamethasone.
Absorption and Excretion study in minipigs	Single dose of calcipotriol and betamethasone in a gel formulation compared to an ointment formulation 4F minipigs per dose group (fasted) Dermal application to 2x150cm^2 patch on the upper flanks 1) [^{3}H]-calcipotriol (50 µg/g) + betamethasone (500 µg/g) 2) Calcipotriol (50 µg/g) + [^{3}H]-betamethasone (500 µg/g) Sampling at 0, 6, 24, 48, 72, 96, 120, 144, 168 h Cumulative excretion of total (% of dose applied) radioactivity in urine, faeces, liver, serum, whole blood, dosed skin, cage wash	1) *Transdermal absorption of calcipotriol:* gel 2.4%,ointment 3.5% Highest level found in cage wash (gel) and faeces (ointment) 2) *Transdermal absorption of betamethasone:* gel 2.6%, ointment 3.5% Highest level found in faeces (gel, ointment) and cage wash (ointment) Absorption of calcipotriol and betamethasone from the gel and the ointment was similar. The main route of excretion was via the faeces for both calcipotriol and betamethasone.

Clinical Pharmacology

The atrophogenic potential and dermal tolerance of calcipotriol and betamethasone dipropionate gel was compared with that of Diprosone* (Schering Plough Ltd.) ointment, containing 0.5 mg/g betamethasone (as dipropionate) and the calcipotriol and betamethasone dipropionate gel vehicle in a randomized, controlled right/left comparison on the forearm of healthy subjects. Sonography showed a similar reversible decrease in skin thickness for calcipotriol and betamethasone dipropionate gel (10.6%) and Diprosone* ointment (11.1%) when applied once daily for 4 weeks. However, a statistically significant skin thinning effect was seen with calcipotriol and betamethasone dipropionate gel compared to the gel vehicle. This effect was reversible at the end of treatment. There were no clinical signs of skin atrophy, telangiectasia or erythema.

The vasoconstrictive effects of calcipotriol and betamethasone dipropionate gel were compared to Diprosone*, a potent WHO group III steroid. Calcipotriol and betamethasone dipropionate gel was not bioequivalent to Diprosone* ointment as the 90% CI for the colorimetric skin blanching response ratio was 0.64 to 0.95, i.e. outside the pre-defined interval of 0.80 to 1.25. The vasoconstrictive effect of calcipotriol and betamethasone dipropionate gel was lower than that of Diprosone* ointment. Based on the results of this study, the potency of betamethasone dipropionate in calcipotriol and betamethasone dipropionate gel is not expected to exceed that of a potent WHO group III steroid.

TOXICOLOGY

Toxicologic studies are summarized briefly here and in more detail by species in tabular form following this section.

Acute and Long-term Toxicity

Calcipotriol: Despite the intended topical use of calcipotriol in the treatment of psoriasis, most of the toxicological studies were performed using the oral route of administration. This was done to assure maximum exposure to the compound. From these studies it was evident that toxicity associated with the administration of pharmacologically excessive doses of calcipotriol was due to the calcitropic activity of the compound. The maximum doses were 54 mcg/kg/day in rats, 18

mcg/kg/day in minipigs and 3.6 mcg/kg/day in dogs. In the acute, subacute and chronic toxicity studies the main signs of toxicity were loss of bodyweight, increases in plasma or serum calcium, creatinine and urea, renal toxicity and soft tissue calcifications. These changes resulted from the exaggerated absorption of calcium and phosphorous from the intestine and are characteristic of vitamin D overdosage. The kidney was the main target organ of toxicity and tubular lesions and calcifications were apparent after prolonged hypercalcemia in all species investigated.

Calcipotriol and Betamethasone Dipropionate: Two dermal studies of 4-week and 9-month duration respectively were conducted in minipigs to assess local and systemic toxicity. In both studies, minipigs received daily topical administration of calcipotriol and betamethasone ointment at doses of 2/20, 10/100 and 50/500 mcg/g. The main observation was erythema of varying severity seen primarily in the high dose group. There were no systemic effects after 4 weeks, however after 9 months systemic absorption resulted in dermal atrophy of non-treated skin.

Local Tolerance

Calcipotriol: Dermal tolerability of calcipotriol was limited to a slight-to-moderate skin irritative effect. The studies performed with calcipotriol ointment showed that the incidence and severity of skin irritation was slightly less in the calcipotriol-treated group than in the placebo ointment group. The formulation of the ointment base is analogous to that employed for a number of corticosteroids available for the treatment of psoriasis. Skin thinning, as seen with corticosteroid application, was not observed with the calcipotriol ointment.

***Calcipotriol and Betamethasone Dipropionate*:** Two dermal tolerability studies with calcipotriol and betamethasone ointment were conducted in rabbits. In the first study, no skin irritation was observed and only slight irritation attributed primarily to calcipotriol was observed in the second study. A gradual reduction in skin thickness was observed over 6 weeks which was attributed to betamethasone. However, the stratum corneum of rabbit skin is much thinner than that of humans and rabbits are very sensitive to skin irritants. Similar results were obtained for two dermal tolerability studies in rabbits using a gel formulation of calcipotriol and betamethasone. In addition, an eye irritation study was conducted in rabbits using a single ocular application (approx. 100 mg) of calcipotriol and betamethasone gel. There was a temporary pink

discolouration of the orbital ring and ptosis observed which cleared within 6 hrs.

Reproduction and Mutagenicity

Animal reproduction studies have not been conducted with calcipotriol and betamethasone dipropionate gel.

Calcipotriol: Reproduction studies have shown that calcipotriol has no effect on fertility in male and female rats nor on their F1 generation progeny. Teratogenicity studies were performed by the oral route in rats and rabbits. In rats, a few minor deviations occurred in pregnant rats given calcipotriol at doses up to 54 mcg/kg/day during days 6-15 of gestation, attributable to the pharmacological effects of calcipotriol on calcium metabolism. No teratogenic effects were observed. In rabbits, at 36 mcg/kg/day of calcipotriol from day 6-18 of gestation, maternal toxicity was observed, characterized by deaths, body weight losses, reduced food intake, increased post-implantation loss, reduced mean fetal weight and increased minor ossification changes. At 12 mcg/kg/day slight signs of maternal toxicity (body weight loss, reduced food intake, maternal death or abortion in 2/18 animals) and reduced mean fetal weight were seen. Peri- and post-natal development studies indicated that calcipotriol had no toxic effects on the F1 or F2 generation. There was also no evidence for a mutagenic or clastogenic potential with calcipotriol.

Betamethasone: Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction 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.

Carcinogenicity

Calcipotriol: A dermal carcinogenicity study in mice showed no indications of increased carcinogenic risks. Calcipotriol solution was applied topically for up to 24 months at doses of 3, 10 and 30 mcg/kg/day (corresponding to 9, 30 and 90 mcg/m^2/day). The high-dose was considered to be the Maximum Tolerated Dose for dermal treatment of mice with calcipotriol.

Survival was decreased at 10 and 30 mcg/kg/day; particularly in the males. The reduced survival was associated with an increased incidence of obstructive uropathy, most probably caused by treatment-related changes in the urinary composition. This is an expectable effect of treatment with high doses of calcipotriol or other vitamin D analogues. There were no dermal effects and no dermal or systemic carcinogenicity.

Betamethasone: No carcinogenicity studies have been performed.

Photo(co)carcinogenicity

Calcipotriol: In a study where albino hairless mice were repeatedly exposed to both ultraviolet radiation (UVR) and topically applied calcipotriol for 40 weeks at the same dose levels as in the dermal carcinogenicity study (see above), a reduction in the time required for UVR light to induce the formation of skin tumours was observed (statistically significant in males only), suggesting that calcipotriol may enhance the effect of UVR to induce skin tumours.

Betamethasone: No photocarcinogenicity studies have been performed with betamethasone dipropionate alone.

Calcipotriol and Betamethasone Dipropionate: Albino hairless mice were treated repeatedly with either calcipotriol solution or calcipotriol and betamethasone gel, followed by irradiation with UVR. The study showed a similar enhancing effect of calcipotriol alone on the photobiological response of the skin but indicated no effect of the calcipotriol and betamethasone combination.

LONG-TERM TOXICITY OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

STUDY TYPE	ANIMAL / STRAIN	DOSE/ ROUTE / DURATION	IMPORTANT FINDINGS
Repeat-dose	Minipigs (Göttingen) 3M/3F per group	Calcipotriol/betamethasone ointment: 0, 2/20, 10/100, 50/500 mcg/g Once daily topical application for 4 weeks	Dose-dependent irritant effect on the skin at 50/500 mcg/g with no signs of systemic toxicity. NOAEL: 10/100 mcg/g calcipotriol/betamethasone Very slight erythema in the 10/100 mcg/g group; slight to moderate erythema in the 50/500 mcg/g group.
Repeat-dose	Minipigs (Göttingen) 5M/5F per group	Calcipotriol/betamethasone ointment: 0, 2/20, 10/100, 50/500 mcg/g Once daily topical application for 9 months	Moderate to severe persistent erythema in the 10/100 and 50/500 mcg/g groups, respectively. Tendency towards treatment-related elevated urinary Ca and PO4 (calcipotriol effect) and decreased adrenal organ weight and dermal atrophy (betamethasone effect). NOAEL: 2/20 mcg/g calcipotriol/betamethasone
Dose-range finding	Mice (albino hairless) 10F per group	1) Untreated 2) Calcipotriol solution: 0, 3, 10, 30 mcg/mL 3) Calcipotriol and betamethasone gel: 0/0, 3/30, 10/100 mcg/g Once daily dermal application for 4 weeks	Skin reactions (30 mcg/mL and 30/300 mcg/g) including erythema, oedema, flaking, wrinkling and thickening and body weight losses (30/300 mcg/g) that resulted in termination of these groups after 6 d of administration. Dose-dependent skin thinning and reduction in body weight in the calcipotriol and betamethasone gel formulation groups. Clinical findings (supported by histopathological evaluation) of dose-dependent skin inflammation for both formulations, including modification of the calcipotriol effects by the addition of betamethasone.

OTHER TOXICITY OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

STUDY TYPE	ANIMAL / STRAIN	DOSE/ ROUTE / DURATION	IMPORTANT FINDINGS
Photosafety	Mice (albino hairless) 24F per group	1) Untreated (UVR dose:0, 1, 2) 2) Calcipotriol solution: 0 (vehicle), 1, 3, 10 mcg/mL (UVR dose:1) 3) Calcipotriol and betamethasone gel: 0/0 (vehicle), 1/10, 3/30, 10/100 mcg/g (UVR dose:1) 4) Triamcinolone gel: 5000 mcg/g (UVR dose:1) Once daily dermal application for 4 weeks UVR dose 1 MED_{if}=2 standard erythema doses	*Calcipotriol solution vehicle*: no UVR-induced histopathological changes. *Calcipotriol solution (1-10 mcg/mL):* elicited skin irritation and changes in histo-pathological markers indicating possible enhancement of photocarcinogenesis. *Calcipotriol/betamethasone gel vehicle:* elicited cutaneous gross and histopatho- logical changes indicative of irritation. *Calcipotriol/betamethasone gel (1/10-10/100 mcg/g):* no UVR-induced histopatho-logical changes. Gross reactions and microscopic findings in the skin of these mice were similar to mice given triamcinolone (shown in published data to not enhance photo-carcinogenesis).
Photosafety	Mice (albino hairless) 12F per group	1) Untreated 2) Calcipotriol solution: 0 (vehicle) 1, 3, 10 mcg/mL 3) Calcipotriol and betamethasone gel: 0/0 (vehicle), 1/10, 3/30, 10/100 mcg/g 4) Triamcinolone gel: 5000 mcg/g Once daily dermal application for 4 weeks All mice exposed to a series of 6 UVR doses. UVR dose: 0.5, 0.7, 1.0, 1.4, 2.0, 2.8 MED_i	Repeated administration of calcipotriol solution (up to100 mcg/mL) or calcipotriol betamethasone gel (up to 10/100 mcg/mL) followed by a single series of UVR exposures, had no adverse effect on the observational minimal erythema dose (MED_o). Skin reactions, clinical observations and body weight effects were consistent with the known effects of these test formulations in this test system. The MED_o, skin reaction and clinical observations for the 10/100 mcg/g calcipotriol/betamethasone group were similar to the group given 5000 mcg/g triamcinolone. Hence, there was no evidence of UVR-induced cutaneous inflammation from repeated topical administration of calcipotriol solution or calcipotriol and betamethasone gel.

LOCAL TOLERANCE OF CALCIPOTRIOL AND BETAMETHASONE DIPROPIONATE

STUDY TYPE	ANIMAL	DOSE/ ROUTE/ DURATION	IMPORTANT FINDINGS
Dermal tolerability	Rabbit (n=6)	Once daily application of 100 mg calcipotriol and betamethasone dipropionate ointment and 100 mg vehicle ointment on separate skin areas for 6 weeks.	No skin irritation was observed. Histopathological changes consisting of squamous metaplasia of pilosebaceous tissue and comedogenic activity attributable to the ointment vehicle were observed.
Dermal tolerability	Rabbit (n=6)	Once daily application of 100 mg of calcipotriol and betamethasone dipropionate ointment calcipotriol (50 mcg/g), betamethasone (as dipropionate) (0.5 mg/g), and vehicle ointment on separate skin areas for 6 weeks.	Slight skin irritation attributed primarily to calcipotriol was observed. Histopathological changes consisting of squamous metaplasia of pilosebaceous tissue and comedogenic activity attributable primarily to the ointment vehicle were observed.
Dermal tolerability (non-occlusive)	Rabbit (NZW) (6M per group)	Once daily topical application of 100 mg of calcipotriol and betamethasone dipropionate gel-and gel vehicle for 3 weeks	Mild to moderate skin irritation. Mean score for erythema (max=4) on day 18 was gel vehicle 1.0 and calcipotriol / betamethasone dipropionate gel 0.67. Irritation was ascribed to the vehicle. Calcipotriol/betamethasone dipropionate gel treated rabbits showed decreased weight gain and smaller adrenal glands.
Dermal tolerability (non-occlusive)	Rabbit (NZW) (6M per group)	Once daily topical application of 100 mg of calcipotriol and betamethasone dipropionate gel and gel vehicle for 4 weeks	Mild to moderate skin irritation. Mean score for erythema (max-4) on day 28 was gel vehicle 1.0 and calcipotriol / betamethasone dipropionate gel 1.5. Irritation was ascribed to one or both active components and the vehicle. Treated and untreated areas showed a marked decrease in skin fold thickness (betamethasone effect). A temporary weight loss due to betamethasone was seen in the first 2 weeks of the study.
Eye irritation	Rabbit (NZW) (5M)	Single ocular application of 2 drops (approx. 100 mg) of calcipotriol and betamethasone dipropionate gel	The mean score of ocular lesions (max) based on 24, 48 and 72 hr assessments: cornea opacity 0 (4); iris lesion 0(2); conjunctiva erythema 0(3); conjunctivae chemosis 0(4). The only effects observed were ptosis and slight pink discolouration of the orbital ring at 1 hr after treatment but these effects disappeared within 6 hrs.

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44. Product Monograph DOVOBET® Gel, LEO Pharma Inc., Submission No. 234060, Date of Revision February 25, 2020.

PART III: CONSUMER INFORMATION

[Pr]Taro-Calcipotriol / Betamethasone Gel
calcipotriol and betamethasone dipropionate gel

This leaflet is part III of a three-part "Product Monograph" published when Taro-Calcipotriol / Betamethasone Gel was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Taro-Calcipotriol / Betamethasone Gel. Contact your doctor or pharmacist if you have any questions about this drug.

ABOUT THIS MEDICATION

What the medication is used for:

Taro-Calcipotriol / Betamethasone Gel is applied to the skin in the treatment of patients 18 years and older with:

- Moderate to severe psoriasis on the scalp for up to 4 weeks, and
- Mild to moderate psoriasis plaques on the body for up to 8 weeks.

What it does:

Taro-Calcipotriol / Betamethasone Gel contains two medicines in one product; calcipotriol (a vitamin D-like substance) and betamethasone (a corticosteroid) that work together to control psoriasis.

Psoriasis lesions are areas of inflamed skin where the production of skin cells is too rapid. This creates red, scaly, thick patches (plaques) of skin. Treatment is targeted at reducing signs of redness and scaling and symptoms such as itching.

Calcipotriol helps to bring the rate of skin cell growth back to normal. Betamethasone works to reduce inflammation (redness, swelling and itching).

When it should not be used:

Do not use Taro-Calcipotriol / Betamethasone Gel:

- if you are allergic to any of the ingredients or the container of Taro-Calcipotriol / Betamethasone Gel
- if you have problems with high calcium levels in your body
- if you have skin infections caused by viruses (e.g. cold sores, chicken pox), a fungus (e.g. athlete's foot, ringworm), bacteria, parasites (e.g. scabies), tuberculosis or syphilis
- on skin areas with perioral dermatitis (red mouth rash), ichthyosis (dry, scaly skin), acne (pimples), rosacea (flushed facial skin),
- on skin areas that have ulcers, open sores, thin skin, easily damaged veins, stretch marks
- to treat other types of psoriasis
- if you have severe liver disease
- if you have severe kidney disease
- in the eyes or on itchy skin of the genital or anal area.

What the medicinal ingredients are:

Calcipotriol monohydrate and betamethasone dipropionate.
Each gram of gel contains 50 mcg calcipotriol (as monohydrate) and 0.5 mg betamethasone (as dipropionate)

What the nonmedicinal ingredients are:

Alpha-tocopherol, butylated hydroxytoluene, hydrogenated castor oil, mineral oil and polyoxypropylene stearyl ether.

What the container ingredients are:

polyethylene

What dosage forms it comes in:

Taro-Calcipotriol / Betamethasone Gel is an almost clear, colourless to slightly off-white gel. Available in cartons of 1 or 2 bottles of 60 g.

WARNINGS AND PRECAUTIONS

BEFORE you use Taro-Calcipotriol / Betamethasone Gel talk to your doctor or pharmacist if you:

- have diabetes
- have skin infections
- use other medicines that contain corticosteroids or calcipotriol (Vitamin D).
- are pregnant or planning to get pregnant
- are breast feeding

Taro-Calcipotriol / Betamethasone Gel is not recommended in children and adolescents under 18 years of age.

Calcipotriol in Taro-Calcipotriol / Betamethasone Gel may increase the risk of developing skin cancer caused by ultraviolet radiation (UVR).

While using Taro-Calcipotriol / Betamethasone Gel, you should avoid excessive exposure to natural or artificial sunlight (UVR) such as phototherapy, tanning beds, sunlamps, etc.

Do not use Taro-Calcipotriol / Betamethasone Gel on your face, skin folds (e.g. groin, armpit, under the breast or in the creases of the buttocks), genitals or on open sores on the skin. Do not use Taro-Calcipotriol / Betamethasone Gel in or near the eyes. Taro-Calcipotriol / Betamethasone Gel may cause eye irritation and irritation of facial skin.

Do not bandage, apply a dressing or wrap the treated skin area after applying Taro-Calcipotriol / Betamethasone Gel on your body.

If used on the scalp, do not cover your scalp with a shower cap, bandages or dressings after applying Taro-Calcipotriol / Betamethasone Gel.

If required, your doctor may recommend a blood test to check your calcium level or the functioning of your adrenal gland.

INTERACTIONS WITH THIS MEDICATION

Before using Taro-Calcipotriol / Betamethasone Gel tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those you can buy without a prescription, especially medicines that contain a corticosteroid and/or calcipotriol.

PROPER USE OF THIS MEDICATION

Always use Taro-Calcipotriol / Betamethasone Gel exactly as your doctor has told you.

Usual dose:

Apply Taro-Calcipotriol / Betamethasone Gel once daily to the affected areas. Treatment on the body may be continued for up to 8 weeks. Treatment on the scalp may be continued for up to 4 weeks. After discontinuing treatment, if your psoriasis flares up again later, you can begin a new treatment cycle.

The maximum daily dose is 15 g per day, or 100 g per week of Taro-Calcipotriol / Betamethasone Gel and/or any other products containing calcipotriol. The total body surface area treated, including scalp and body should not exceed 30%.

Before Applying Taro-Calcipotriol / Betamethasone Gel:

- Use only on areas of your skin affected by psoriasis and not on skin that does not have psoriasis.
- If applying to your scalp, you don't need to wash your hair before applying Taro-Calcipotriol / Betamethasone Gel.

SHAKE bottle well before use. Remove cap.

Using Taro-Calcipotriol / Betamethasone Gel on the body:

Apply a sufficient amount of gel on affected area to cover plaque with an even layer.

It may help to spread the gel in two perpendicular lines forming a cross within a plaque (i.e. cross unit) to ensure the right amount of drug is applied for the size of the plaque.

Do not spread too thinly. Be sure to apply a sufficient amount of gel to cover the plaque. Massage gently until gel has been absorbed into skin.

Using Taro-Calcipotriol / Betamethasone Gel on the scalp:

- Comb dry hair first to remove loose psoriasis scales.
- For long hair, gently part your hair to reveal affected scalp area.
- Squeeze a pea-size drop of Taro-Calcipotriol / Betamethasone Gel onto your fingertip.
- Apply gel with your finger to affected scalp areas that have visible psoriasis.
- For a larger area of plaque or for very thick hair, you may need to re-part hair to expose neighbouring psoriasis area. Repeat until the entire affected area (or plaque) is covered with an even layer of gel.

After applying Taro-Calcipotriol / Betamethasone Gel:

- Wash your hands well after applying Taro-Calcipotriol / Betamethasone Gel
- It is important to leave treatment areas uncovered. Do not bandage, apply a dressing or wrap the skin or scalp.
- Do not wash your body/hair immediately after application in order to achieve optimal effect. Taro-Calcipotriol / Betamethasone Gel should be left on body/scalp until absorbed.
- Taro-Calcipotriol / Betamethasone Gel should not be applied 12 hours before or after colouring, perming or any chemical hair treatments. To help avoid irritation, always ask your doctor about using any hair treatments with scalp psoriasis.

Overdose:

If you think you have applied too much Taro-Calcipotriol / Betamethasone Gel, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to use Taro-Calcipotriol / Betamethasone Gel use it as soon as you remember. Next time, follow your regular application routine. It's important not to use Taro-Calcipotriol / Betamethasone Gel more than once a day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect with use of Taro-Calcipotriol / Betamethasone Gel on the scalp as well as on the body is itching. Other less common effects reported for Taro-Calcipotriol / Betamethasone Gel include: burning sensation of the skin, skin pain or irritation, inflammation of hair root, hair loss, rash (with or without pustules), skin infection, eye irritation, redness, acne, dizziness, dry skin, headache, facial swelling, flushing, migraine, outer ear infection, sinus infection, increased blood calcium level, increased blood parathyroid hormone and decreased blood phosphorus level.

Side effects caused by long term use of corticosteroid-containing products such as Taro-Calcipotriol / Betamethasone Gel include: thinning of the skin, stretch marks or surface veins, changes in hair growth, red mouth rash, skin rash with inflammation, small white spots, lightening of skin colour.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
Uncommon: Worsening of psoriasis (red, scaly, thick patches of skin)	✓	
Rare: Pustular psoriasis (red area with yellowish pustules, headache, fever, chills, arthralgia, malaise, anorexia, nausea)		✓
Rare: Adrenal effects (weakness, increased urination/thirst, fatigue, weight loss), cataracts, infections	✓	
Very Rare: Allergic reaction (rash, itching, swelling, trouble breathing, dizziness)		✓
Very Rare: High blood calcium (fatigue, depression, mental confusion, anorexia, nausea, vomiting, constipation, increased urination/thirst)		✓

This is not a complete list of side effects. For any unexpected effects while taking Taro-Calcipotriol / Betamethasone Gel, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15 °C to 30 °C. Do not refrigerate. Protect from light by keeping the bottle in the carton between applications.

- Keep Taro-Calcipotriol / Betamethasone Gel out of the reach and sight of children and pets.
- Use the medicine within 6 months of first opening the bottle.
- Do not use Taro-Calcipotriol / Betamethasone Gel after the expiry date on the label (EXP).

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Taro-Calcipotriol / Betamethasone Gel:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.taro.ca, or by calling 1-800-268-1975.

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