PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrENSTILAR®

calcipotriol and betamethasone dipropionate aerosol foam

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

Topical Antipsoriatic Agent
Vitamin D Analogue / Corticosteroid
DO5AX52

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 3.1 Recommended Dose and Dose Adjustment	04/2022
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ENSTILAR (calcipotriol and betamethasone dipropionate) is indicated for the topical treatment of psoriasis vulgaris in adults for up to 4 weeks.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety of ENSTILAR for the treatment of mild to severe psoriasis vulgaris has been evaluated in pediatric patients aged 12 to 17 years treated once daily for up to 4 weeks (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Efficacy in pediatric patients aged 12 to 17 years is supported by efficacy data from adequate and well-controlled studies in the adult population age 18 years and above. The safety and efficacy of ENSTILAR in pediatric patients less than 12 years of age have not been evaluated. The use of ENSTILAR in pediatric patients less than 12 years of age is not recommended (see WARNINGS AND PRECAUTIONS, Special Populations).

1.2 Geriatrics

Geriatrics (> *65* years of age): No overall differences in safety or effectiveness of ENSTILAR were observed between the geriatric and younger subjects (See WARNINGS AND PRECAUTIONS, Special Populations).

2 CONTRAINDICATIONS

ENSTILAR is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Known hypersensitivity to any ingredient in the formulation or to components of the container.
- Patients with known disorders of calcium metabolism.
- Skin areas having viral lesions (e.g. herpes or varicella), fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis.
- Skin areas having perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wounds.
- Erythrodermic and pustular psoriasis.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Treatment Dose

ENSTILAR should be applied to the affected area once daily for up to 4 weeks. Once daily therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, reassessment may be necessary.

If it is necessary to restart treatment after this period due to signs of relapse, once daily treatment for up to 4 weeks may be re-initiated.

A two-second application delivers approximately 0.5 g if the actuator is fully depressed. As a guide, 0.5 g of foam is sufficient to cover an area of skin roughly corresponding to the surface area of one patient's palm (which is also equivalent to ~1% BSA affected by psoriasis).

In clinical trials (LP0053-1001, LEO 90100-7, LEO 90100-35) the average amount of ENSTILAR applied was roughly 30 g per week in subjects with a mean baseline BSA of around 7%.

Maintenance dose

Patients who have responded to ENSTILAR treatment (once daily for up to 4 weeks) may continue using ENSTILAR as maintenance therapy: applied twice weekly, 2-3 days apart, to areas previously affected by psoriasis vulgaris, for up to 52 weeks.

If signs of a relapse occur, once daily treatment should be re-initiated for up to 4 weeks as described above. Patients who respond to once daily treatment may continue with maintenance therapy twice weekly.

Maximum Dose

The maximum daily dose of ENSTILAR should not exceed 15 g, i.e., one 60 g can would last for at least 4 days of treatment. 15 g corresponds to the amount of foam released from the can when the actuator is fully depressed for approximately one minute.

For treatment dose, the maximum weekly dose should not exceed 100 g. If using other calcipotriol containing medical products concomitantly, the total weekly dose of all calcipotriol containing medical products, including ENSTILAR, should not exceed 100 g. The total body surface area treated, including scalp should not exceed 30%.

Pediatrics (< 18 years of age)

The safety of ENSTILAR has been evaluated in pediatric patients age 12 to 17 years treated once daily for up to 4 weeks (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Efficacy in pediatric patients aged 12 to 17 years is supported by efficacy data from adequate and well-controlled studies in the adult population age 18 years and above. 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. The safety and efficacy of ENSTILAR in pediatric patients less than 12 years of age have not been evaluated. The use of ENSTILAR in pediatric patients less than 12 years of age is not recommended.

Geriatrics (≥ 65 years of age)

No overall differences in safety or effectiveness of ENSTILAR were observed between the geriatric and younger subjects.

4.4 Administration

- The can should be shaken before each use.
- ENSTILAR should be applied by holding the can at least 3 cm from the skin.
- If used on the scalp, ENSTILAR should be sprayed into the palm of the hand and then applied to affected scalp areas with the fingertips. Hair washing instructions are provided in the package leaflet.
- ENSTILAR should be used in a well-ventilated area.
- Inhalation should be avoided.
- The product may feel cool when sprayed on the skin due to evaporation of the propellants.
- The foam can be sprayed holding the can in any orientation except horizontally.
- ENSTILAR should be rubbed gently into the affected skin areas.
- The hands should be washed after using ENSTILAR (unless ENSTILAR is used to treat the hands) to avoid accidentally spreading to other parts of the body as well as unintended drug absorption on the hands.
- It is recommended not to take a shower or bath immediately after application of ENSTILAR.

4.5 Missed Dose

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

5 OVERDOSAGE

Usage of ENSTILAR above the recommended dose may cause elevated serum calcium which should subside when treatment is discontinued. The symptoms of hypercalcemia include polyuria, constipation, muscle weakness, confusion and coma.

Excessive prolonged use of topical corticosteroid containing products, including ENSTILAR, may result in adrenocortical suppression which is usually reversible. Symptomatic treatment may be indicated. In case of chronic toxicity, corticosteroid treatment must be discontinued gradually.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Aerosol Foam; 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate)	all-rac-α-tocopherol, butylhydroxytoluene, liquid paraffin, polyoxypropylene-11-stearyl ether and white soft paraffin

Description

ENSTILAR is a white to off-white, opalescent liquid in a pressurized can. After spraying, a white to off-white flat, non-expanding foam is formed. The foam has the appearance of a non-expanding foam that gradually disintegrates after spraying. The product is alcohol-free and odourless.

Propellants: butane, dimethyl ether

Packaging: Aluminium can with an inner lacquer, equipped with a continuous valve and actuator. The can contains 60 g of ENSTILAR, not including the amount of propellants.

Pack sizes: 60 g and 2 x 60 g. Not all pack sizes may be marketed.

7 WARNINGS AND PRECAUTIONS

General

There is no experience with the use of ENSTILAR in guttate psoriasis.

Long term use of corticosteroids may increase the risk of local and systemic adverse reactions. Treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see ADVERSE REACTIONS).

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, use in pediatric patients, and use in patients with liver failure.

Application of topical corticosteroid products including ENSTILAR 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).

In a maximum use (up to 113 g/week) trial in adult subjects (N=35) with extensive psoriasis vulgaris treated with ENSTILAR for 4 weeks, a trend for decreased cortisol response to ACTH with increased dose was identified, but no clinically meaningful adrenal suppression was

observed (see ACTION AND CLINICAL PHARMACOLOGY).

Hypercalcemia and hypercalciuria have been observed with the use of ENSTILAR. If hypercalcaemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized (see WARNINGS AND PRECAUTIONS/Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic

There are no adequate and well controlled studies of ENSTILAR use in patients with hepatic impairment. As calcipotriol and corticosteroids undergo hepatic metabolism, ENSTILAR should be used with caution in patients with severe hepatic impairment.

Monitoring and Laboratory Tests

Treatment with ENSTILAR 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, ENSTILAR 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, and ACTION AND CLINICAL PHARMACOLOGY).

Ophthalmologic

ENSTILAR is not for ophthalmic use. ENSTILAR may cause eye irritation. Avoid contact with the eyes.

Renal

There are no adequate and well controlled studies of ENSTILAR use in patients with renal impairment. As corticosteroids undergo renal excretion, ENSTILAR should be used with caution in patients with severe renal impairment.

Skin

ENSTILAR contains betamethasone dipropionate, which is a potent World Health Organization (WHO) group III corticosteroid. Concurrent treatment with other corticosteroids on the same treatment area should be avoided.

ENSTILAR should not be used on the face, axillae, flexures, groin or genitals. The patient must be instructed in the correct use of ENSTILAR to avoid accidental transfer or application to these regions or to the mouth, mucous membranes or eyes. Hands must be washed after each application to avoid accidental transfer to these areas as well as unintended drug absorption on the hands (see DOSAGE AND ADMINISTRATON).

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 ENSTILAR (see ADVERSE REACTIONS).

When treating psoriasis with topical corticosteroid containing products, including ENSTILAR, for a prolonged period of time, it is recommended that treatment be interrupted periodically. There may be a risk of generalised pustular psoriasis or rebound psoriasis when discontinuing treatment.

Concomitant skin infections should be treated with an appropriate antimicrobial agent. If the infection worsens, ENSTILAR should be discontinued until the infection has been adequately treated (see CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of ENSTILAR use during pregnancy has not been established. When given orally in animals, calcipotriol was associated with fetotoxicity (such as incomplete bone ossification and skeletal abnormalities). Studies in animals with orally administered betamethasone dipropionate have shown reproductive toxicity, including teratogenicity (see TOXICOLOGY, Reproduction and Teratogenicity).

A number of epidemiological studies in pregnant women have not revealed congenital anomalies among infants born to women treated with topical corticosteroids during pregnancy. However, the use of large amounts of topical corticosteroids over extensive parts of the body during pregnancy may be associated with low birth weight.

As the potential risk of using ENSTILAR during pregnancy is uncertain, ENSTILAR should be used for the shortest possible duration, in the smallest needed amounts.

7.1.2 Breast-feeding

The safety of calcipotriol and/or topical corticosteroids for use in nursing women has not been established. Betamethasone passes into breast milk, but it is not known if topical application of corticosteroid containing products, including ENSTILAR, can lead to sufficient systemic absorption to produce detectable quantities in breast milk. Caution should be exercised when prescribing ENSTILAR to women who breastfeed. The patient should be instructed not to use ENSTILAR on the breast when breastfeeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety of ENSTILAR for the treatment of psoriasis vulgaris has been evaluated in pediatric patients aged 12 to 17 years treated once daily for up to 4 weeks (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Efficacy in pediatric patients aged 12 to 17 years is supported by efficacy data from adequate and well-controlled studies in the adult population age 18 years and above. 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. The safety and efficacy of ENSTILAR in pediatric patients less than 12 years of age have not been evaluated. The use of ENSTILAR in pediatric patients less than 12 years of age is not recommended.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Of the total number of subjects in the controlled clinical studies of ENSTILAR (LP0053-1001, LEO 90100-7, LEO 90100-35), 97 were 65 years or older, of which 21 were 75 years or older.

In a post-approval clinical study (LP0053-1004), the efficacy and safety of long-term maintenance therapy with ENSTILAR was assessed. A total of 134 patients in the initial open-label phase and 63 patients in the ENSTILAR maintenance group were 65 years of age or older.

No overall differences in safety or effectiveness of ENSTILAR were observed between subjects in these age ranges versus younger subjects.

However, since elderly patients have increased skin fragility, a greater frequency of hepatic, renal or cardiac dysfunction, and have concomitant disease or other drug therapy, caution is recommended when using products containing corticosteroids including ENSTILAR.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions during treatment are application site reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The rates of adverse reactions in adult subjects were derived from three randomized, multicenter, prospective vehicle and/or active-controlled clinical trials (LP0053-1001, LEO 90100-7, LEO 90100-35) in more than 1,100 subjects with psoriasis vulgaris. A total of 564 subjects were treated with ENSTILAR once daily up to 4 weeks and the median weekly dose of ENSTILAR was 24.8 g (mean 30.9 g).

There were no adverse reactions that occurred in ≥1% of adult subjects treated with ENSTILAR for up to 4 weeks.

Maintenance Trial

A post-approval clinical study (LP0053-1004) was conducted to assess the efficacy and safety of maintenance therapy. In the open-label phase, 650 patients were treated with ENSTILAR once daily for 4 weeks. In the maintenance phase, 545 patients were randomized to ENSTILAR (N=272) or foam vehicle (N=273) treated twice weekly for up to 52 weeks. Both arms were

treated with ENSTILAR once daily during relapses.

There were no adverse reactions that occurred in ≥1% of subjects treated with ENSTILAR in either the open-label phase, or the maintenance phase.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In one open-label uncontrolled prospective clinical trial, a total of 106 subjects aged 12-17 years with plaque psoriasis of the scalp and body were treated with ENSTILAR once daily for up to 4 weeks. The median and mean weekly dose of ENSTILAR used were similar to the dose used by adult subjects in clinical trials.

No clinically relevant differences between the safety profiles in adults and adolescent populations have been observed. There were no adverse reactions that occurred in ≥1% of pediatric subjects treated with ENSTILAR for up to 4 weeks.

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions are listed by MedDRA SOC. Within each SOC group, adverse reactions are presented in order of decreasing frequency.

Infections and infestations: Folliculitis

Immune system disorders: Hypersensitivity

Metabolism and nutrition disorders: Hypercalcaemia

Skin and subcutaneous tissue disorders: Skin hypopigmentation

General disorders and administration site conditions: Application site pruritus, application site irritation, application site pain including application site burning, rebound effect

Maintenance Trial

Less common adverse reactions (<1%) in the open-label phase included acne, psoriasis, and application site pain. Less common adverse reactions (<1%) in the maintenance phase included pigmentation disorder, folliculitis, and chorioretinopathy in the ENSTILAR arm (receiving maintenance therapy); and rebound psoriasis, psoriasis, pigmentation disorder, pruritus, and folliculitis in the foam vehicle arm (active treatment used only during relapse).

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Less common adverse reactions included acne, erythema, application site pain, and skin reactions (0.9% each).

8.5 Post-Market Adverse Reactions

The following adverse reactions 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.

General disorders and administration site conditions: application site erythema.

8.6 Other Adverse Drug Reactions

The rates of adverse reactions were also derived from another randomized, multicenter, prospective vehicle and active-controlled clinical trial (LP0053-1003) in 463 adult subjects with psoriasis vulgaris. A total of 185 subjects were treated with ENSTILAR once daily for up to 12 weeks.

The only adverse reaction reported in ≥1% subjects treated with ENSTILAR for up to 12 weeks was pruritus (2.7%). Less common aAdverse reactions (<1%) included psoriasis, skin swelling, skin infection, application site pruritus, salivary gland calculus, hyperglycemia, and worsening of insulin resistance.

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone dipropionate, when applied topically:

Calcipotriol: Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, psoriasis aggravated, photosensitivity and hypersensitivity reactions including very rare cases of angioedema and facial oedema.

Very rare cases of hypercalcaemia or hypercalciuria have been reported (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

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 corticosteroids are rare in adults; however, they can be severe. Adrenocortical suppression, cataract, infections, impaired glycaemic control of diabetes mellitus and increase of intra-ocular pressure can occur, especially after long-term treatment. Application of ENSTILAR under occlusion (e.g., plastic, skin folds), on large areas and for prolonged treatment periods may result in increased risk of systemic adverse events and is therefore not recommended (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

No drug interaction studies have been performed with ENSTILAR.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ENSTILAR is a combination of calcipotriol hydrate as a synthetic vitamin D3 analogue and betamethasone dipropionate as a synthetic corticosteroid.

Calcipotriol is a vitamin D receptor agonist which normalizes the proliferation and

differentiation of keratinocytes as potently as 1,25(OH)2D3, the naturally occurring active form of vitamin D. Vitamin D receptor agonists also have an immunomodulatory effect, suppressing activation and differentiation of Th17/Th1 cells while inducing a Th2/Treg response. However, calcipotriol is much less active than 1,25(OH)2D3 in its effect on calcium metabolism.

Betamethasone dipropionate, like other corticosteroids, is a glucocorticoid receptor agonist with anti-inflammatory, immunosuppressive, anti-pruritic and vasoconstrictive properties.

In ENSTILAR, the combination of calcipotriol and betamethasone dipropionate has greater anti-inflammatory and anti-proliferative effects than either component alone.

10.2 Pharmacodynamics

Preclinical Studies

Calcipotriol is a synthetic vitamin D3 analogue which binds to the vitamin D receptor and stimulates vitamin D regulated transcription. *In vitro* pharmacodynamic studies have shown the activity of calcipotriol to be very similar, both qualitatively and quantitatively, to that of 1,25(OH)2D3. Vitamin D receptor agonists have a normalizing effect on human keratinocytes, arresting growth and enhancing differentiation in inappropriately proliferating cells. Vitamin D receptor agonists also have an immunomodulatory effect, suppressing activation and differentiation of Th17/Th1 cells while inducing a Th2/Treg response. Through these effects on T cells, calcipotriol may interrupt the pro-inflammatory feedback loop that drives the inflammatory hyperproliferative response of keratinocytes in psoriasis.

In-vivo however, the effects of calcipotriol were significantly different from those of 1,25(OH)2D3. 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)2D3. The low activity of calcipotriol on calcium metabolism is attributed to a rapid metabolic degradation of the active compound.

Betamethasone dipropionate in ENSTILAR is a synthetic corticosteroid. Corticosteroids suppress the immune system, particularly pro-inflammatory cytokines and chemokines, thereby inhibiting T-cell activation. At the molecular level, corticosteroids act via the intracellular glucocorticoid receptor and the anti-inflammatory function is due to transrepression of pro-inflammatory transcription factors such as nuclear factor κB, activator protein-1, and interferon regulatory factor-3.

Clinical Studies

The vasoconstrictor activity (skin blanching response) of ENSTILAR observed in a study in healthy volunteers indicates that the potency of ENSTILAR is higher than that of the marketed calcipotriol plus betamethasone dipropionate ointment formulation, but less than clobetasol propionate cream.

The effect of ENSTILAR on the HPA axis and calcium metabolism were evaluated in a maximum use (up to 113 g/week) trial in adult subjects (N=35) with extensive psoriasis involving at least 30% of the scalp and, in total, 15-30% of the body surface area. Treatment consisted of once daily application on the scalp and body for 4 weeks. There was a trend for decreased cortisol response to ACTH with increased dose, however, no patient demonstrated adrenal suppression,

defined as cortisol level ≤18mcg/dL 30-minute post-stimulation, after 4 weeks of treatment. There was no evidence of change of calcium metabolism and serum, and urinary calcium levels were within the normal range for all subjects.

In addition, effects of once-daily application of ENSTILAR for 4 weeks on calcium metabolism in adult subjects (N=564) with psoriasis vulgaris were examined in three randomized, multicenter, prospective vehicle- and/or active-controlled clinical trials. There were no changes in mean serum or urinary calcium levels. However, elevated serum calcium levels outside the normal range were observed in 3 subjects and elevated urinary calcium levels outside the normal range were observed in 17 subjects.

The effects of once-daily application of ENSTILAR for 12 weeks on calcium metabolism were studied in adult subjects (N=185) with psoriasis vulgaris. Serum calcium levels above the normal range were observed in 1 subject at week 4 which normalized at week 8 and week 12. Urinary calcium: creatinine ratio above the normal range occurred in 1 subject at week 4 (which normalized at weeks 8 and 12), 5 subjects at week 8, and 6 subjects at week 12. No clinically significant changes in mean albumin-corrected serum calcium or spot urinary calcium: creatinine ratio were seen.

Maintenance Therapy

In the open-label phase, a subset of 66 subjects was evaluated for adrenal response to ACTH challenge. These subjects had moderate to severe psoriasis vulgaris and their mean extent of psoriasis was 15.0% (range: 10.0–30.0%) of BSA. HPA axis suppression (a cortisol level ≤18 mcg/dL at 30 minutes after ACTH challenge) was observed in 1 patient (1.5%) after 4 weeks of once daily treatment with ENSTILAR. In the maintenance phase, subjects who achieved treatment success (PGA score of clear or almost clear with at least a 2-grade improvement from baseline), were randomized to receive ENSTILAR or foam vehicle twice weekly for up to 52 weeks. Subjects experiencing a relapse were treated with ENSTILAR once daily for 4 weeks. Subjects who regained a PGA score of clear or almost clear continued randomized treatment. A total of 40 subjects in the maintenance treatment group (ENSTILAR or vehicle twice weekly) were assessed for HPA axis suppression. HPA axis suppression (a cortisol level ≤18 mcg/dL at 30 minutes after ACTH challenge) was observed in 2 patients (9.5%) in the ENSTILAR group and 1 patient (5.3%) in the foam vehicle group at Week 52.

There were no clinically relevant effects on serum or urinary calcium in this trial.

Pediatrics

In one adolescent Phase 2 open-label uncontrolled prospective clinical trial, a total of 106 subjects aged 12-17 years with plaque psoriasis of the scalp and body were treated with ENSTILAR once daily for up to 4 weeks. The mean age was 14.2 years. The majority of subjects had moderate disease. The mean baseline extent of psoriasis on the body was 10.4% of BSA and on the scalp was 50.6% of scalp area.

The effects on calcium metabolism were investigated in all 106 adolescent subjects at Week 4. No cases of hypercalcaemia and no clinically relevant changes in serum or urinary calcium were reported.

The effect on the HPA axis was assessed by the adrenal response to ACTH challenge in a subset of 33 patients with moderate psoriasis and no weekly dosing limit. The mean baseline extent of psoriasis on the body was 16.3% of BSA and on the scalp was 55.5% of scalp area. The mean amount of ENSTILAR applied was 47 g per week. After 4 weeks of treatment with ENSTILAR, HPA axis suppression (a cortisol level ≤18 mcg/dL at 30 minutes after ACTH challenge) was observed in 3 patients (9%). None of these cases had any clinical manifestations.

10.3 Pharmacokinetics

Absorption: An in vitro permeation study using pig ear skin compared the penetration of calcipotriol and betamethasone dipropionate at 2, 6 and 21 hrs after application of ENSTILAR and a calcipotriol/betamethasone dipropionate ointment. ENSTILAR resulted in greater penetration of both calcipotriol (3-fold) and betamethasone dipropionate (2-fold) into the skin than the ointment. The amounts measured in the recipient fluid were low, but overall, they were also higher with ENSTILAR than with the ointment formulation.

Plasma levels of calcipotriol and betamethasone dipropionate and their main metabolites were measured after 4 weeks of once daily application of ENSTILAR to 15-30% of the body surface area (scalp and body). Calcipotriol was quantifiable in 1 of 35 (2.9%) subjects and its main metabolite, MC1080, in 3 of 35 (8.6%) subjects. The plasma concentrations of calcipotriol and MC1080 ranged between <50 - 55.9 pg/mL and <20 - 26.6 pg/mL, respectively. Betamethasone dipropionate was quantifiable in 5 of 35 (14.3%) subjects and its main metabolite, betamethasone 17-propionate (B17P), was quantifiable in 27 of 35 (77.1%) subjects. The plasma concentrations of betamethasone dipropionate and B17P ranged between <30 - 81.1 pg/mL and <30 - 1133 pg/mL, respectively.

Distribution: In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

Metabolism: Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised.

Calcipotriol metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriol are less potent than the parent compound. 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 primarily in the liver to betamethasone 17-propionate and betamethasone, including the 6β-hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.

Elimination: The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice).

Pre-clinical Studies

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. Autoradiography studies performed in rats established that calcipotriol concentrations were highest in the liver, kidney and intestine. No drug-related radioactivity was present 24 hours after administration of 3H-calcipotriol.

Following oral administration to rats at 0.02, 0.06 and 0.2 mg/kg/day, the concentration of betamethasone dipropionate was below the lower limit of quantification (75 pg/mL) in all samples. The Cmax values of the main metabolite betamethasone 17-propionate were 3 – 5 fold higher in female than in male rats and the AUCinf values were generally 5 fold higher in female than in male rats. In all dose groups and in both genders the tmax of betamethasone 17-propionate was 0.5 hours and the half-life was 0.28–0.46 hours with no difference between genders.

Following dermal administration of calcipotriol/betamethasone dipropionate ointment to minipigs, the transdermal absorption of 3H-calcipotriol and 3H-betamethasone dipropionate was 2.1-3.5% and 3.3-3.5%, respectively, of the administered dose.

Special Populations and Conditions

- **Hepatic Insufficiency**

  As calcipotriol and corticosteroids undergo hepatic metabolism, ENSTILAR should be used with caution in patients with severe hepatic impairment.

- **Renal Insufficiency**

  As corticosteroids undergo renal excretion, ENSTILAR should be used with caution in patients with severe renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store ENSTILAR between 15° to 30 °C.

Contents under pressure. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 50°C.

Keep in a safe place out of the reach and sight of children.

After opening, the product should be stored at room temperature (15° to 30°C) and should be used within 6 months, and before the expiry date.

12 SPECIAL HANDLING INSTRUCTIONS

The propellants in ENSTILAR are very flammable. Do not use in presence of open flame or spark.

PART II: SCIENTIFIC INFORMATION

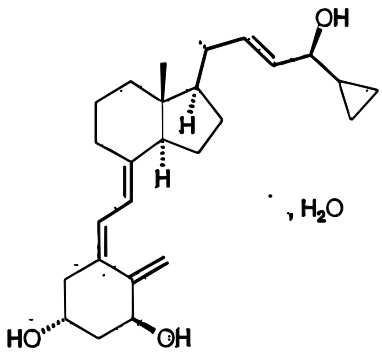
13 PHARMACEUTICAL INFORMATION

Drug Substance

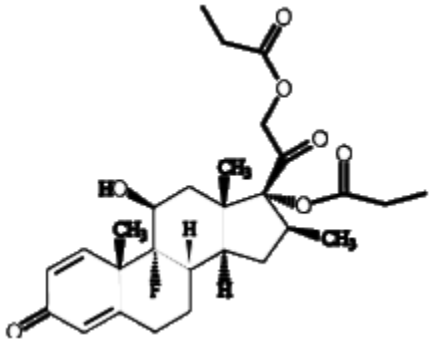
	Calcipotriol hydrate	Betamethasone dipropionate
Proper name (I.N.N.):		
Chemical name:	9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol, 24-cyclo-propyl-, monohydrate, (1α,3β,5Z,7E,22E,24S)	9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate
Alternative chemical name:	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	Pregna-1,4-diene-3,20-dione,9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-(11β,16β)
Laboratory code name:	MC 903, hydrate MC 903, H_20	433 or 433/M
Molecular formula:	$C_{27}H_{40}O_3$, H_2O	$C_{28}H_{37}FO_7$
Molecular mass:	430.6	504.6
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 hydrate

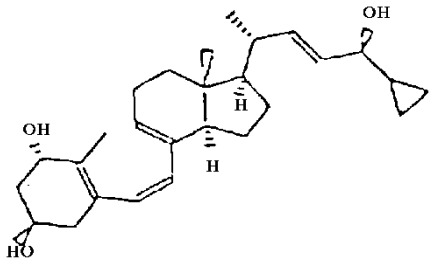


Betamethasone dipropionate



Physicochemical properties :

	Calcipotriol hydrate	Betamethasone dipropionate
Physical form:	White or almost white crystalline substance.	White or almost white odourless 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.	



14 CLINICAL TRIALS

The efficacy and safety of once daily use of ENSTILAR has been investigated in four randomized, double-blind or investigator-blind, clinical trials in adults (Table 1, Study # LP0053-1001, LEO 90100-7, LEO 90100-35 and LP0053-1003).

Maintenance therapy

The efficacy and safety of maintenance treatment with Enstilar was investigated in a randomised, double-blind vehicle-controlled trial (Table 1, Study #LP0053-1004). Subjects were treated once daily with open-label ENSTILAR for 4 weeks and responders were then randomised to receive ENSTILAR or foam vehicle twice weekly for up to 52 weeks. Subjects in both treatment arms experiencing a relapse were treated once daily with ENSTILAR for 4 weeks, and those responding then continued randomised treatment (Table 1).

14.1 Trial Design and Study Demographics

Table 1. Summary of Study Demographics and Trial Design

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
LP0053-1001	Phase 3, multi-centre, randomized (3:1), double-blind, 2-arm; ENSTILAR vs. foam vehicle	Topical, once daily application to body, 4-week duration	426 (323 used ENSTILAR; 103 used vehicle)	50.0 yrs (18-87 yrs)	M 253 F 173
LEO 90100-7	Phase 3,POC, multi-centre, randomized (1:1:1), double-blind, 3-arm; ENSTILAR vs. BDP* vs. calcipotriol	Topical, once daily application to body and scalp, 4-week duration	302 (100 used ENSTILAR; 101 used BDP in foam vehicle; 101 used calcipotriol in foam vehicle)	49.0 yrs (20-85 yrs)	M 170 F 132

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
LEO 90100-35	Phase 2, multi-centre, comparative, randomized (3:1:3:1), investigator-blind, 4-arm: ENSTILAR vs. foam vehicle vs. Dovobet® Ointment vs. ointment vehicle	Topical, once daily treatment on body, 4-week duration	376 (141 used ENSTILAR; 49 used foam vehicle; 135 used Dovobet® Ointment; 51 used ointment vehicle)	50.4 yrs (21-88)	M 234 F 142
LP0053-1003	Phase 3, multi-centre, randomized (4:4:1:1) investigator-blind, 4-arm: ENSTILAR vs. Dovobet® Gel vs. foam vehicle vs. gel vehicle	Topical, once-daily treatment on body, 12-week duration	463 (185 used ENSTILAR; 188 used Dovobet® Gel; 47 used foam vehicle; 43 used Gel vehicle)	54.1 yrs (18–86)	M 295 F 168
LP0053-1004	Phase 3, 52-week maintenance, international, multi-site, randomised, vehicle-controlled, double-blind, 2-arm, parallel group	Initial open-label phase: topical, once daily treatment on trunk and/or limbs, 4-week duration Maintenance phase: randomised in 1:1 ratio of subjects who achieved treatment success at Week 4: topical, twice weekly 3 or 4 days apart, 52 weeks duration with 8 weeks follow-up phase. Rescue medication once-daily for 4 weeks with confirmed relapse.	650 (used Enstilar in open-label phase; 623 completed the phase) 545 (out of 623 were randomised to receive Enstilar or vehicle in maintenance phase; 251 completed the phase)	Open-label phase: 51.8 yrs (19-84) Maintenance phase: 52.2 yrs (19-84)	Open-label phase: M: 424 F: 226 Maintenance phase: M: 372 F: 173

**BDP: betamethasone dipropionate*

The patient populations included in the four clinical trials that support the efficacy and safety of ENSTILAR were adult subjects with psoriasis vulgaris on the body (i.e. trunk and limbs) in LP0053-1001, LEO 90100-7, LEO 90100-35, LP0053-1003, also on the scalp in LEO 90100-7, where 2% - 30% of body surface area (BSA) was affected.

Each of the four trials included subjects with a range of disease severity levels at baseline, from 'mild' to 'severe' according to the Physician's Global Assessment (PGA) of disease severity. The PGA is made using a 5-point scale (clear, almost clear, mild, moderate and severe) based on the

average psoriatic lesion. Approximately 64 to 75% of subjects across trials had 'moderate' disease (PGA), and up to 10% of subjects had 'severe' disease on the body at baseline. In all four clinical trials, the mean baseline BSA affected by psoriasis was roughly 7%. The subjects also had a modified psoriasis area severity index (m-PASI) of at least 2. The m-PASI is a composite score assessing severity (erythema, scale and induration) and affected area (excluding face and skin folds).

The primary endpoint for trials LP0053-1001, LEO 90100-7, and LEO 90100-35 was subjects with 'treatment success' ('clear' or 'almost clear' for subjects with at least moderate disease at baseline, 'clear' for subjects with mild disease at baseline) according to the PGA at Week 4. The primary endpoint for LP0053-1003 was subjects with 'treatment success' according to the PGA at Week 4 for ENSTILAR and at Week 8 for Dovobet® Gel.

Maintenance therapy

Trial LP0053-1004 included subjects aged ≥18 years with psoriasis vulgaris for at least 6 months involving the trunk and/or limbs involving 2 - 30% of the BSA and a PGA of at least mild. Baseline characteristics for subjects in the maintenance phase can be found in the table below.

Table 2. Disease-related baseline characteristics

	LP0053-1001 (N=426)	**LEO 90100-7 (N=302)**	**LEO 90100-35 (N=376)**	**LP0053-1003 (N=463)**	**LP0053-1004 (N=545) ***
Baseline disease severity (PGA)					
Mild	65 (15.3%)	41 (13.6%)	63 (16.8%)	122 (26.3%)	58 (10.6%)
Moderate	319 (74.9%)	230 (76.2%)	292 (77.7%)	295 (63.7%)	447 (82.0%)
Severe	42 (9.9%)	31 (10.3%)	21 (5.6%)	46 (9.9%)	40 (7.3%)
Mean BSA (range)	7.5% (2–30%)	7.1% (2 – 28%)	7.5% (2-30%)	7.3% (2-30%)	8.3 (1.0 – 38.0)
Mean m-PASI (range)	7.5 (2.0-47.0)	7.6 (2.0-28.0)	6.8 (2.0-22.6)	7.0 (2.0-28.0)	7.8 (2.0 – 28.0)

*Randomised subjects.

14.2 Study Results

Results for the 'treatment success' of body at Week 4, as measured by PGA, showed ENSTILAR to be statistically significantly more effective than the comparators and responses were observed in all categories of baseline disease severity.

Table 3. Percentage of subjects with 'treatment success' according to the PGA of the body at Week 4.

	ENSTILAR	Foam vehicle	BDP* in foam vehicle	Calcipotriol in foam vehicle	Dovobet® Ointment	Ointment vehicle	Dovobet® Gel#	Dovobet® Gel vehicle#
LP0053-1001	(N=323) 53.3 %	(N=103) 4.8 %	-	-	-	-	-	-
LEO 90100-7	(N=100) 45.0 %	-	(N=101) 30.7 %	(N=101) 14.9 %	-	-	-	-
LEO 90100-35	(N=141) 54.6 %	(N=49) 6.1 %	-	-	(N=135) 43.0 %	(N=51) 7.8 %	-	-
LP0053-1003	(N=185) 38.3%	(N=47) 4.3%	-	-	-	-	(N=188) 22.5%#	(N=32) 0%

**BDP: betamethasone dipropionate*
#Treatment success at week 8

In LEO 90100-7 the effect of ENSTILAR on scalp psoriasis was investigated as the percentage of subjects with 'treatment success' according to the PGA of the scalp at Week 4.

Table 4. Percentage of subjects with 'treatment success' according to the PGA of the scalp at Week 4.

	ENSTILAR	BDP in foam vehicle	Calcipotriol in foam vehicle
LEO 90100-7	(N=100) 53.0 %	(N=101) 47.5 %	(N=101) 35.6 %

ENSTILAR was statistically significantly more effective compared to calcipotriol and also associated with a higher rate of treatment success than BDP but this comparison did not reach statistical significance.

The effect of once daily use of ENSTILAR on itch and itch-related sleep loss was investigated in LP0053-1001 by assessments with a horizontal visual analogue scale (VAS) where the range was from 0 millimeters (mm) (no itch at all; no sleep loss at all) to 100 mm (worst itch you can imagine; worst possible sleep loss). Only subjects who reported itch and itch-related sleep loss at baseline were evaluated.

Figure 1. Percentage of subjects achieving at least 70% reduction in itch compared to baseline in LP0053-1001

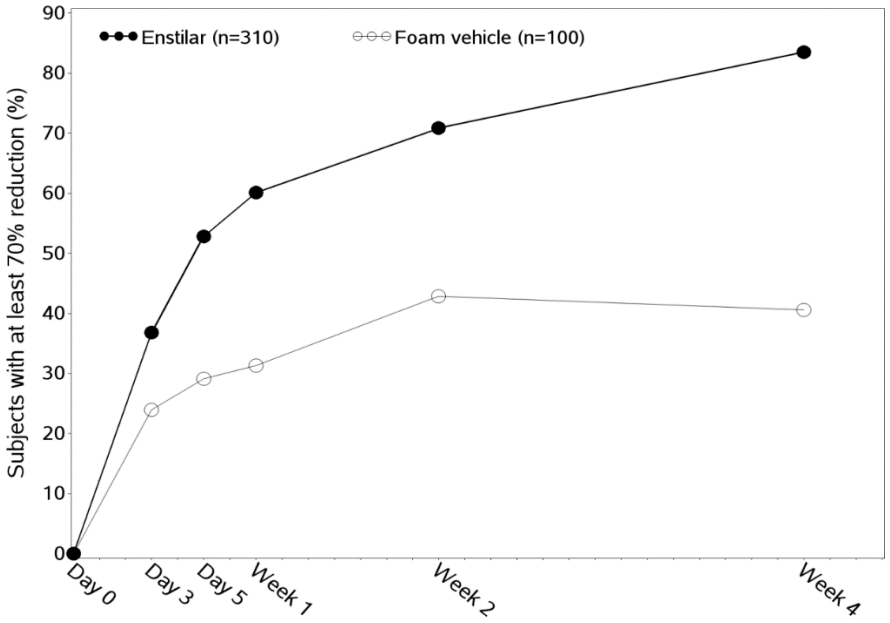
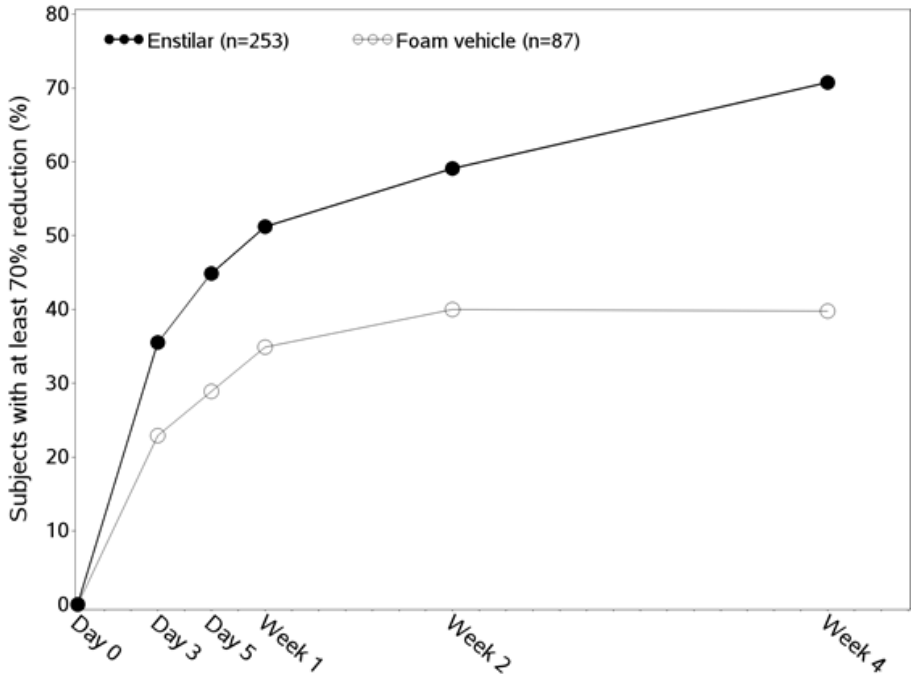


Figure 2. Percentage of subjects achieving at least70% reduction in itch-related sleep loss compared to baseline in LP0053-1001



Statistically significant differences of at least 70% reduction in both itch and itch-related sleep loss were observed in favor of subjects receiving ENSTILAR compared to those receiving foam vehicle from Day 3 and throughout the treatment period.

Across three clinical trials (LP0053-1001, LEO 90100-7, LEO 90100-35), the average amount of ENSTILAR applied was roughly 30 g per week. In the trial LP0053-1003, the average amount of ENSTILAR applied during the first 4 weeks of treatment was approximately 24 g per week.

Quality of life was investigated in LP0053-1001 by means of the generic EQ-5D-5L and the dermatologically specific DLQI. Statistically significantly greater improvement in quality of life, measured by DLQI, was demonstrated for subjects receiving ENSTILAR compared to those receiving foam vehicle from Week 1 and throughout the treatment period. Measured by EQ-5D-5L, a statistically significantly greater improvement in favor of subjects receiving ENSTILAR compared to those receiving foam vehicle was demonstrated at Week 4.

Maintenance therapy

Subjects (responders at Week 4 of open-label phase) on maintenance treatment with Enstilar had longer time to first relapse, greater proportion of days in remission during the trial, and fewer relapses than subjects using foam vehicle. The table below presents an overview of the effect on relapse in this trial.

Table 4. Summary of efficacy up to 52 weeks of maintenance treatment in LP0053-1004.

Endpoint	Observed data in the trial		Statistical analysis results (N=521)*	
	Maintenance + relapse treatment (N=256)	Vehicle + relapse treatment (N=265)	Estimates [95% CI]	p-value
Primary: Time to first relapse	Median time to first relapse=56 days	Median time to first relapse=30 days	HR=0.57 [0.47; 0.69] (Reduction of 43% [31%; 53%])	p<0.001

Secondary: Proportion of days in remission	Median proportion of days=69.3%	Median proportion of days=56.6%	DP=11% [8%;14%] (Increase of 41 [29; 53] days)	p<0.001
Secondary: Number of relapses	Relapse rate (relapses per 100 PYE) =300.4 Median number of relapses: 2.0	Relapse rate (relapses per 100 PYE) =468.4 Median number of relapses: 3.0	RR=0.54 [0.46;0.63] (Reduction of 46% [37%; 54%])	p<0.001

*Statistical analysis compared maintenance treatment + relapse treatment with Vehicle + relapse treatment

CI: Confidence interval; DP: Difference in proportion of days per year; HR: Hazard-ratio; N: number of subjects in full analysis set; RR: Rate-ratio; PYE: Patient-years of exposure

15 NON-CLINICAL TOXICOLOGY

Acute and Long-term Toxicology

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.

Betamethasone dipropionate: Betamethasone dipropionate is a widely used and well-characterized corticosteroid which has been shown to have metabolic and toxicological effects typical for corticosteroids. Oral administration of betamethasone dipropionate for up to 13 weeks in rats produced expected signs of toxicity, including body weight loss, leucopenia/lymphopenia and dose-related decreases in thymus and spleen weights along with pathological findings in these organs. Reduced body weight gain was observed in females at all dose levels (0.02, 0.06 and 0.2 mg/kg) and in high- and mid-dose males. The number of white blood cells was decreased (leucopenia) along with a decreased number of lymphocytes (lymphopenia) in the mid- and high-dose groups. In a 13-week dermal mouse study, adverse effects (reduced body weight gains or pathological findings in the spleen and thymus) were observed at dosages above 10 µg/kg/day. The NOAEL in this study was considered to be 3.3 µg/kg/day. In general, results from repeat dose toxicity studies demonstrated that adverse effects were associated with the known pharmacological activity of betamethasone dipropionate which exhibits immunosuppressive properties.

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 dipropionate 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

A 4-week local dermal tolerance study was performed using four minipigs to assess any differences in irritant potential of calcipotriol and betamethasone dipropionate foam and the vehicle. The frequency of treatment was once daily topical non-occlusive application for 4 weeks. The treatment with calcipotriol and betamethasone dipropionate foam resulted in very slight, clinically and microscopically visible skin irritation and in minimal multifocal epidermal atrophy. No skin changes were seen after treatment with the corresponding foam vehicle.

Reproduction and Teratogenicity

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

Calcipotriol: Studies with oral doses of up to 54 mcg/kg/day of calcipotriol indicated no impairment of fertility or general reproductive performance in male and female rats, nor on their F1 generation progeny.

Teratogenicity studies with calcipotriol were performed by the oral route in rats and rabbits. In rabbits, increased maternal toxicity (body weight loss, reduced food intake, maternal death and abortion) and fetal toxicity (reduced mean fetal weight) were noted at a dosage of 12 mcg/kg/day. A dosage of 36 mcg/kg/day resulted in similar maternal and fetal toxicity characteristics; in addition, a significant increase in the incidence of incomplete ossification of the pubic bones and forelimb phalanges of fetuses was observed. In a rat study, a dosage of 54 mcg/kg/day resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles were most likely due to the effect of calcipotriol upon calcium metabolism. The estimated maternal and fetal no-adverse effect levels (NOAEL) in the rat and rabbit are 18 mcg/kg/day and 4 mcg/kg/day, respectively.

An oral peri- and post-natal development study was conducted with rats. Pregnant Wistar rats were dosed daily with calcipotriol at exposures of 0, 6, 18 or 54 mcg/kg/day from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameters, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate: Studies in male rats at oral doses of up to 200 mcg/kg/day, and in female rats at oral doses of up to 1000 mcg/kg/day, of betamethasone dipropionate indicated no impairment of fertility.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at dosages of 156 mcg/

kg/day and 2.5 mcg/kg/day, respectively. The abnormalities observed included umbilical hernia, exencephaly, skeletal malformations and cleft palate.

An oral peri- and post-natal development study was conducted with rats. Betamethasone dipropionate was evaluated for effects when orally administered to pregnant rats from gestation day 6 through day 20 postpartum at dosages of 0, 100, 300, and 1000 mcg/kg/day. Reduced mean maternal body weight and prolonged gestation were detected in the treatment groups. Moreover, reduction in offspring survival, reduced body weight, and impaired righting reflex was observed. No effects on the ability of pups to learn were observed post-weaning, and the ability of the offspring of treated rats to reproduce was not affected.

Mutagenicity

Calcipotriol: Calcipotriol did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test.

Betamethasone dipropionate: Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

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. 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.

A 104-week oral carcinogenicity study was conducted with calcipotriol in male and female rats at doses of 1, 5 and 15 mcg/kg/day. Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day. A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 5 or 15 mcg/kg/day and males receiving 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males receiving 15 mcg/kg/day. No other statistically significant differences in tumor incidence were observed when compared to control. The relevance of these findings to patients is unknown.

Betamethasone dipropionate: When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2 and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males, no significant changes in tumor incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day, no significant changes in tumor incidence were observed when compared to control.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrENSTILAR®

calcipotriol and betamethasone dipropionate aerosol foam

Read this carefully before you start using **Enstilar®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Enstilar®**.

What is Enstilar® used for?

Enstilar® is used to treat adults with a skin condition called psoriasis vulgaris.

How does Enstilar® work?

Enstilar® contains two medicines, calcipotriol and betamethasone, that work together to control psoriasis.

Psoriasis causes areas of inflamed skin where skin cells grow too fast. This creates red, scaly, thick patches (plaques) of skin.

Calcipotriol is a vitamin D-like substance that helps to bring the rate of skin cell growth back to normal. Betamethasone is a corticosteroid that works to reduce inflammation (redness, swelling and itching).

What are the ingredients in Enstilar®?

Medicinal ingredients: calcipotriol (as monohydrate) and betamethasone (as dipropionate).

Non-medicinal ingredients: all-rac-α-tocopherol, butylhydroxytoluene, liquid paraffin, polyoxypropylene-11-stearyl ether and white soft paraffin.

Propellants: butane, dimethyl ether.

Enstilar® comes in the following dosage forms:

Aerosol foam; 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate).

After spraying, the foam will not expand and will disintegrate gradually. The product is alcohol-free and has no odor.

Do not use Enstilar®:

- if you are allergic to any of the ingredients in Enstilar® or the container (aluminium).
- if you have a condition that affects your calcium levels.
- if you have a skin infection caused by a virus, fungus, bacteria or parasite.
- if you have a skin condition related to tuberculosis.
- on areas with perioral dermatitis (rash around the mouth).

- on areas with thin skin, stretch marks or fragile veins.
- on areas with dry scaly skin caused by a condition called ichthyosis.
- on areas that have acne (pimples, redness), rosacea (red flushed facial skin), ulcers or wounds.
- if you have a type of psoriasis with severe inflammation called erythrodermic psoriasis, or a type of psoriasis with pus-filled blisters called pustular psoriasis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use Enstilar®. Talk about any health conditions or problems you may have, including if you:

- have diabetes
- have a skin infection or if skin areas with psoriasis become infected
- use other medicines that contain corticosteroids or calcipotriol
- are pregnant or planning to get pregnant
- are breastfeeding
- are over 65 years old
- have problems with your kidneys or liver

Other warnings you should know about:

- Do not use Enstilar® on your face, under the arms, in the groin area, in skin folds/creases or on areas of broken skin.
- Do not bandage, cover or wrap the treated skin area after applying Enstilar®.
- Enstilar® is not recommended for use in children.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Enstilar®:

The use of Enstilar® with other medicines has not been studied. However, since medicines can interact with each other, tell your healthcare professional if you are using other medicines to treat your psoriasis. In particular, tell them if you are using medicines that contain corticosteroids.

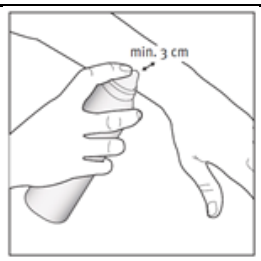
How to use Enstilar®:

Proper use:

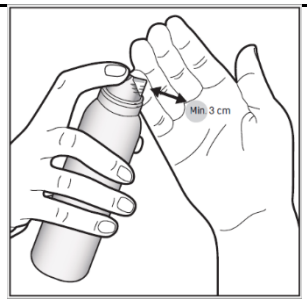
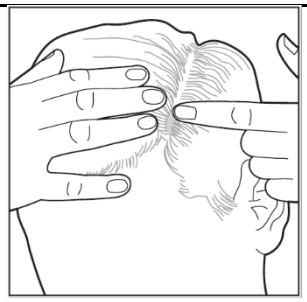
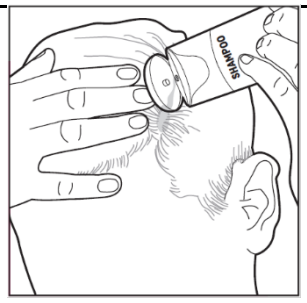
- Use only on areas of your skin affected by psoriasis. If you accidentally get foam on normal skin, wipe it off before it spreads too far.
- Wash or rinse off foam if applied to the following areas by accident:
    - Eyes, mouth, genitals, or breasts (if you are breast feeding).

- Use Enstilar® in well-ventilated area and avoid breathing it in.
- Spraying Enstilar® for about 2 seconds is enough to cover an area of skin that is about the size of a patients' palm.
- After applying the medication, put the cap back on the can. This will prevent accidental spraying when not in use.
- Leave the treated areas uncovered. Do not bandage, cover or wrap the skin. Enstilar® should be left on the body until fully absorbed. For optimal effect, do not shower or take a bath immediately after applying the foam.
- After applying the foam, avoid contact with fabrics which are easily stained by grease (e.g. silk).

A. When Used on the Body:

1. Shake the can for a few seconds before use.	
2. Hold the can at least 3 cm (1.2 inches) from the skin and spray.	
3. The foam can be sprayed by holding the can in any position except sideways. The product may feel cool when sprayed on the skin from the propellants evaporating.	
4. Gently rub the foam into the affected skin areas.	
5. Wash your hands well after using Enstilar® (unless you are using it to treat your hands). This will avoid spreading the foam to other parts of your body (especially the face, mouth and eyes) by accident.	

B. When Used on the Scalp:

1. Comb the hair to remove any loose scales.	
2. Shake the can for a few seconds before use.	
3. Hold the can at least 3 cm away. Spray directly into the palm of your hand. The foam can be sprayed holding the can in any position except sideways. The product may feel cool when sprayed on the skin from the propellants evaporating.	
4. Scoop the foam onto your finger and apply it directly to the affected areas. Minimize applying into the hair to make it easier to wash it out. Gently rub the foam into the scalp.	
5. Wash your hands well after using Enstilar®. This will avoid spreading the foam to other parts of your body (especially the face, mouth and eyes) by accident.	
When you wash your hair, the following instructions might be useful:	
1. Apply a mild, nonmedicated shampoo to **dry hair.** Focus on the areas where the foam was applied. It is easier to remove Enstilar® when shampoo is applied to dry hair. Water dilutes the cleansing effect of the shampoo.	
2. Massage the shampoo into the **dry hair/scalp**. Leave the shampoo on the scalp for a couple of minutes before washing.	
3. Rinse thoroughly with water.	
4. Repeat normal shampooing if necessary.	

Usual dose:

There are two different dosage schedules for Enstilar®. Treatment dose is to treat your psoriasis and maintenance dose is to delay or reduce the risk of your psoriasis coming back after treatment.

Treatment dose:

- Apply once daily to affected areas for up to 4 weeks. Spraying Enstilar® for about 2 seconds is enough to cover an area of skin that is about the size of your palm. This is equal to about 0.5 g.
- **Do not** use more than 15g/day. 15 g corresponds to the amount of foam released when Enstilar® is sprayed for about one minute. One 60g can should last for at least 4 days. The maximum weekly dose of Enstilar® (including other products containing calcipotriol) is 100g.
- Stop using Enstilar® once you are satisfied with the results. If no improvement is seen after 4 weeks of treatment, go see your doctor. **Do not** use Enstilar® for more than 4 consecutive weeks, unless directed by your doctor.
- If your psoriasis comes back, you can restart Enstilar® as outlined above and contact your doctor as soon as possible to review your treatment.

Maintenance dose:

- Once your psoriasis has cleared or almost cleared, your doctor may recommend to continue using Enstilar® two times a week for up to one year. Between applications there should be 2 to 3 days without treatment (e.g. apply Monday and Thursday). **Do not** use more than 15g/day on application days.
- If symptoms reappear, use Enstilar® once daily as outlined above (treatment dose) and contact your doctor as soon as possible to review your treatment. If your psoriasis clears or almost clears, go back to using Enstilar® two times a week (maintenance dose).

Overdose:

If you think you, or a person you care for, have used too much Enstilar®, 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 Enstilar®, use it as soon as you remember. Next time, follow your regular application routine. Do not use Enstilar® more than once a day.

What are possible side effects from using Enstilar®?

These are not all the possible side effects you may have when using Enstilar®. If you experience any side effects not listed here, tell your healthcare professional.

- itching, irritation or pain
- drying, reddening, or swelling of the skin

- a burning or stinging sensation
- various types of skin rashes (dermatitis)
- acne
- small white spots
- thinning skin, stretch marks or surface veins
- red and swollen hair follicles
- changes in hair growth
- skin infection
- lightening of skin colour
- facial rash and swelling

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop using drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Worsening of psoriasis: red, scaly, thick patches of skin		✓	
RARE			
Pustular psoriasis: chills, feeling unwell, fever, headache, joint pain, loss of appetite, nausea, red area with yellowish pimples			✓
Adrenal effects: fatigue, increased urination/thirst, problems controlling blood sugar levels, weakness, weight loss		✓	
VERY RARE			
Allergic reaction: dizziness, itching, rash, swelling, trouble breathing			✓
Hypercalcaemia (high calcium levels in the blood): constipation, depression, fatigue, increased urination/thirst, loss of appetite, mental confusion, nausea, vomiting			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.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.

Storage:

- Store Enstilar® between 15° to 30°C.
- After opening, the product should be stored at room temperature (15° to 30°C) and should be used within 6 months, and before expiry date.
- Contents under pressure. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 50°C. The product is very flammable. Do not use in presence of open flame or spark.
- Keep out of reach and sight of children.

If you want more information about Enstilar®:

- 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.leo-pharma.ca, or by calling 1-800-263-4218.

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