

**CALCIPOTRIENE 0.005% AND BETAMETHASONE DIPROPIONATE 0.064% -
calcipotriene and betamethasone dipropionate ointment
Sandoz Inc.**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment safely and effectively. See Full Prescribing Information for calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.

**Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% Ointment for TOPICAL use only.
Initial U.S. Approval: 2006**

----- **INDICATIONS AND USAGE** -----

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is a vitamin D analogue and corticosteroid combination product indicated for the topical treatment of psoriasis vulgaris in adults 18 years of age and older (1.1).

Limitations of Use:

Do not use on face, axillae, or groin (1.2)

Do not use if skin atrophy is present at the treatment site (1.2)

----- **DOSAGE AND ADMINISTRATION** -----

- Apply calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment to affected area(s) once daily for up to 4 weeks.
- The maximum weekly dose should not exceed 100g. Treatment of more than 30% body surface area is not recommended (2).
- Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is not for oral, ophthalmic, or intravaginal use.

----- **DOSAGE FORMS AND STRENGTHS** -----

Ointment 0.005%/0.064%

Each gram of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment contains 50 mcg of calcipotriene and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) (3).

----- **CONTRAINDICATIONS** -----

None (4).

----- **WARNINGS AND PRECAUTIONS** -----

- Hypercalcemia and hypercalciuria have been reported. If it occurs, discontinue treatment until parameters of calcium metabolism normalize (5.1)
- Topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and unmask latent diabetes (5.2)
- Systemic absorption may require evaluation for HPA axis suppression (5.2)
- Modify use should HPA axis suppression develop (5.2)
- Potent corticosteroids, use on large areas, prolonged use or occlusive use may increase systemic absorption (5.3)
- Local adverse reactions with topical steroids may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation and allergic contact dermatitis and may be more likely with occlusive use or more potent corticosteroids (5.3, 6.1)
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids (5.2, 8.4)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions ($\geq 1\%$) are pruritus and scaly rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

1.1 Indication

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is indicated for the topical treatment of psoriasis vulgaris in adults 18 years of age and older.

1.2 Limitations of Use

- Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment should not be applied to the face, axillae or groin.

- Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment should not be used if there is skin atrophy at the treatment site.

2 DOSAGE & ADMINISTRATION

Apply an adequate layer of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment to the affected area(s) once daily for up to 4 weeks. The maximum weekly dose should not exceed 100 g. Treatment of more than 30% body surface area is not recommended. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment should be rubbed in gently and completely. Patients should wash their hands after applying calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS & STRENGTHS

Ointment, 0.005%/0.064%

Each gram of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment contains 50 mcg of calcipotriene and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in off-white to yellow paraffin ointment base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Calcium Metabolism

Hypercalcemia and hypercalciuria have been reported with use of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment. If hypercalcemia or hypercalciuria develop, treatment should be discontinued until parameters of calcium metabolism have normalized. In the trials that included assessment of the effects of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on calcium metabolism following treatment durations of longer than 4 weeks have not been evaluated.

5.2 Effects on Endocrine System

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

HPA axis suppression has been observed with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment [see *Clinical Pharmacology: Pharmacodynamics (12.2)*]. The effects of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the HPA axis following treatment durations of longer than 4 weeks have not been adequately studied.

In a trial of 32 subjects concomitantly treated with Taclonex[®] Scalp Topical Suspension on the scalp and calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the body, adrenal suppression was identified in 5 of 32 subjects (15.6%) after 4 weeks of treatment [see *Clinical Pharmacology: Pharmacodynamics (12.2)*].

Because of the potential for systemic absorption, use of topical corticosteroids may require that

patients be periodically evaluated for HPA axis suppression. 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.

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, to reduce the frequency of application, or to 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.

Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Pediatric patients may be more susceptible to systemic toxicity from use of topical corticosteroids [see *Use in Specific Populations* (8.4)].

5.3 Local Adverse Reactions with Topical Corticosteroids

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

5.4 Allergic Contact Dermatitis with Topical Corticosteroids

Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a *failure to heal* rather than a clinical exacerbation. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

5.5 Allergic Contact Dermatitis with Topical Calcipotriene

Allergic contact dermatitis has been observed with use of topical calcipotriene. Clinical diagnosis of allergic contact dermatitis can be confirmed by patch testing.

5.6 Concomitant Skin Infections

Concomitant skin infections should be treated with an appropriate antimicrobial agent. If the infection persists, calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment should be discontinued until the infection has been adequately treated.

5.7 Skin Irritation

If irritation develops, treatment with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment should be discontinued and appropriate therapy instituted.

5.8 Ultraviolet Light Exposure

Patients who apply calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The data described below reflect exposure to calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment in 2,448 subjects, including 1,992 exposed for 4 weeks, and 289 exposed for 8 weeks. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment was studied primarily in placebo- and active-controlled trials (N = 1,176, and N = 1,272, respectively). The population was 15-97 years old, 61% males and 39% females, mostly white (97%) and had a baseline disease severity ranging from mild to very severe. Most subjects received once daily application, and the median weekly dose was 24.5 g.

The percentage of subjects reporting at least one adverse event was 27.1% in the calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment group, 33.0% in the calcipotriene group, 28.3% in the betamethasone group, and 33.4% in the vehicle group.

Table 1

Adverse Events Reported by ≥1% of Subjects by Preferred Term

	Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% Ointment N = 2,448	Calcipotriene N = 3,197	Betamethasone dipropionate N = 1,164	Vehicle N = 470
Any Adverse Event	663 (27.1)	1055 (33.0)	329 (28.3)	157 (33.4)
Preferred Term	# of subjects (%)			
Pruritis	75 (3.1)	183 (5.7)	38 (3.3)	43 (9.1)
Headache	69 (2.8)	75 (2.3)	44 (3.8)	12 (2.6)
Nasopharyngitis	56 (2.3)	77 (2.4)	34 (2.9)	9 (1.9)
Psoriasis	30 (1.2)	47 (1.5)	14 (1.2)	5 (1.1)
Rash scaly	30 (1.2)	40 (1.3)	0 (0.0)	1 (0.2)
Influenza	23 (0.9)	34 (1.1)	14 (1.2)	6 (1.3)
Upper respiratory tract infection	20 (0.8)	19 (0.6)	12 (1.0)	3 (0.6)
Erythema	15 (0.6)	54 (1.7)	3 (0.3)	5 (1.1)
Application site pruritus	13 (0.5)	24 (0.8)	10 (0.9)	6 (1.3)
Skin irritation	11 (0.4)	60 (1.9)	8 (0.7)	5 (1.1)
Pain	7 (0.3)	12 (0.4)	3 (0.3)	5 (1.1)
Burning sensation	6 (0.2)	30 (0.9)	3 (0.3)	6 (1.3)

A lesional/perilesional adverse event was generally defined as an adverse event located ≤ 2 cm from the lesional border.

Table 2

Lesional/Perilesional Adverse Events Reported by ≥1% of Subjects

	Calcipotriene 0.005% and	Calcipotriene	Betamethasone	Vehicle
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	Betamethasone Dipropionate 0.064% Ointment N = 2,448	N = 3,197	dipropionate N = 1,164	N = 470
Any Adverse Event	213 (8.7)	419 (13.1)	85 (7.3)	76 (16.2)
Preferred Term	# of subjects (%)			
Pruritis	69 (2.8)	170 (5.3)	31 (2.7)	41 (8.7)
Rash scaly	29 (1.2)	38 (1.2)	0 (0.0)	0 (0.0)
Application site pruritus	12 (0.5)	24 (0.8)	10 (0.9)	6 (1.3)
Erythema	9 (0.4)	36 (1.1)	2 (0.2)	4 (0.9)
Skin irritation	9 (0.4)	51 (1.6)	8 (0.7)	5 (1.1)
Burning sensation	6 (0.2)	25 (0.8)	3 (0.3)	5 (1.1)

For subjects who reported lesional/perilesional adverse events, the median time to onset was 7 days for calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, 7 days for calcipotriene, 5 days for betamethasone dipropionate, and 3 days for vehicle.

Other less common reactions (less than 1% but more than 0.1%) were, in decreasing order of incidence, folliculitis, rash papular, rash pustular, and skin hypopigmentation. Skin atrophy, telangiectasia and skin hyperpigmentation were reported infrequently (0.1%).

In a separate trial, subjects (N = 207) with at least moderate disease severity were given calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment intermittently on an “as needed” basis for up to 52 weeks. The median use was 15.4 g per week. The effects of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on calcium metabolism were not studied and the effects on the HPA axis were not adequately studied. The following adverse reactions were reported by 1% or more of the subjects: pruritus (7.2%), psoriasis (3.4%), skin atrophy (1.9%), folliculitis (1.4%), burning sensation (1.4%), skin depigmentation (1.4%), ecchymosis (1.0%), erythema (1.0%) and hand dermatitis (1.0%).

One case of serious flare-up of psoriasis was reported.

6.2 Postmarketing Experience

The following adverse reactions associated with the use of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment have been identified post-approval: pustular psoriasis and rebound effect.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pregnant women were excluded from the clinical studies conducted with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with calcipotriene 0.005% and betamethasone

dipropionate 0.064% ointment. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically.

Teratogenicity studies with calcipotriene were performed by the oral route in rats and rabbits. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12 mcg/kg/day (144 mcg/m²/day); a dosage of 36 mcg/kg/day (432 mcg/m²/day) resulted in a significant increase in the incidence of incomplete ossification of the pubic bones and forelimb phalanges of fetuses. In a rat study, a dosage of 54 mcg/kg/day (324 mcg/m²/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to the effect of calcipotriene upon calcium metabolism. The estimated maternal and fetal no-adverse effect levels (NOAEL) in the rat (108 mcg/m²/day) and rabbit (48 mcg/m²/day) derived from oral studies are lower than the estimated maximum topical dose of calcipotriene in man (460 mcg/m²/day).

Corticosteroids are generally 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 (468 mcg/m²/day) and 2.5 mcg/kg/day (30 mcg/m²/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (about 5950 mcg/m²/day). The abnormalities observed included umbilical hernia, exencephaly and cleft palate.

Two oral peri- and post-natal development studies were conducted with rats: Pregnant Wistar rats were dosed daily with calcipotriene 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 parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

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. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

8.3 NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

Because many drugs are excreted in human milk, caution should be exercised when calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is administered to a nursing woman.

8.4 PEDIATRIC USE

Safety and effectiveness of the use of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment in pediatric patients have not been studied. Because of a higher ratio of skin surface area to body mass, children under the age of 12 years may be at particular risk of systemic adverse effects when they are treated with topical medication [*see Warnings and Precautions (5.2)*].

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles,

headaches, and bilateral papilledema.

8.5 GERIATRIC USE

Of the total number of subjects in the clinical studies of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, approximately 14% were 65 years and older and approximately 3% were 75 years and over.

No overall differences in safety or effectiveness of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment were observed between these subjects and younger subjects. All other reported clinical experience has not identified any differences in response between elderly and younger patients.

8.6 Unevaluated Uses

The safety and efficacy of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated.

The safety and efficacy of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment in patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated.

The safety and efficacy of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

10 OVERDOSAGE

Topically applied calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment can be absorbed in sufficient amounts to produce systemic effects [see *Warnings and Precautions* (5.1, 5.2)].

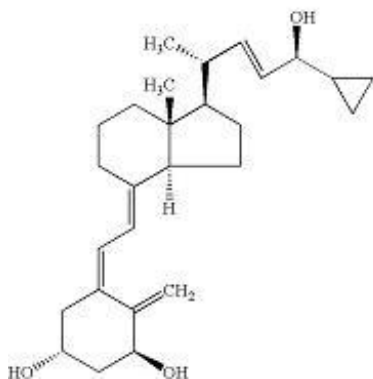
11 DESCRIPTION

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment contains calcipotriene and betamethasone dipropionate.

It is intended for topical use only.

Calcipotriene is a synthetic vitamin D₃ analog.

Chemically, calcipotriene is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochole-5,7,10(19),22-tetraene-1(α),3(β),24-triol, with the empirical formula C₂₇H₄₀O₃, a molecular weight of 412.3, and the following structural formula:

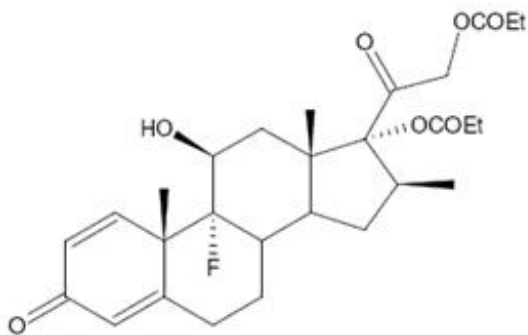


Calcipotriene is a white to almost white crystalline compound.

Betamethasone dipropionate is a synthetic corticosteroid.

Betamethasone dipropionate has the chemical name 9-fluoro-11(β),17,21-trihydroxy-16(β)-

methylpregna-1,4-diene-3,20-dione-17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to almost white odorless powder.

Each gram of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment contains 50 mcg of calcipotriene and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in off-white to yellow paraffin ointment base of caprylic/capric triglycerides, diazolidinyl urea, dl-alpha tocopherol and white petrolatum.

12 CLINICAL PHARMACOLOGY

12.1 MECHANISM OF ACTION

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment combines the pharmacological effects of calcipotriene as a synthetic vitamin D₃ analogue and betamethasone dipropionate as a synthetic corticosteroid.

However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in psoriasis vulgaris are unknown.

12.2 PHARMACODYNAMICS

Vasoconstriction:

In a vasoconstrictor trial, the skin blanching response of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment was consistent with that of a potent corticosteroid.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment was applied once daily for 4 weeks to adult subjects (N = 12) with psoriasis vulgaris to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of eleven subjects tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL.

However in another clinical trial of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, one subject (N = 19) demonstrated adrenal suppression.

HPA axis suppression was evaluated in adult subjects (N=32) 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 of Taclonex Scalp[®] Topical Suspension on the scalp in combination with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the body. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level less than or equal to 18 mcg/dL was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment as per the recommended duration of use (*see*

Dosage and Administration (2.1).

Effects on Calcium Metabolism

In the combination use trial described above, the effects of once daily application of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the body in combination with Taclonex Scalp[®] Topical Suspension on the scalp on calcium metabolism were also examined. Elevated urinary calcium levels outside the normal range were observed in 1 of 35 subjects (2.9%) after 4 weeks of treatment.

12.3 PHARMACOKINETICS

Absorption

The systemic effect of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment in extensive psoriasis was investigated in the trial described above. In this trial, the serum levels of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 weeks (maximum recommended duration of treatment) and also after 8 weeks of once daily application of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the body in combination with Taclonex Scalp[®] Topical Suspension on the scalp. Both calcipotriene and betamethasone dipropionate were below the lower limit of quantification in all serum samples of the 34 subjects evaluated. However, one major metabolite of calcipotriene (MC1080) was quantifiable in 10 of 34 (29.4%) subjects at week 4 and in five of 12 (41.7%) subjects at week 8. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P) was also quantifiable in 19 of 34 (55.9%) subjects at week 4 and seven of 12 (58.3%) subjects at week 8. The serum concentrations for MC1080 ranged from 20-75 pg/mL. The clinical significance of this finding is unknown.

Metabolism

Calcipotriene:

Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Calcipotriene is metabolized to MC1046 (the α,β -unsaturated ketone analogue of calcipotriene), which is metabolized further to MC1080 (a saturated ketone analogue). MC1080 is the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate:

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10 and 30 mcg/kg/day (corresponding to 9, 30 and 90 mcg/m²/day), no significant changes in tumor incidence were observed when compared to control.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.

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 (corresponding to dosages of up to approximately 26 mcg/m²/day and 39 mcg/m²/day, in females and

males, respectively), 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 (corresponding to dosages of approximately 3, 10, and 30 mcg/m²/day), no significant changes in tumor incidence were observed when compared to control.

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

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m²/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m²/day), of betamethasone dipropionate indicated no impairment of fertility.

14 CLINICAL STUDIES

In an international, multi-center, double-blind, vehicle- and active-controlled, parallel-group trial, 1,603 subjects with mild to very severe psoriasis vulgaris on trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, calcipotriene 50 mcg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. The mean age of the subjects was 48.4 years and 60.5% were male. Most subjects had disease of moderate severity at baseline.

Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks). "Absent" disease was defined as no evidence of redness, thickness, or scaling. "Very mild disease" was defined as controlled disease, but not entirely cleared: lesions with some discoloration with absolutely minimal thickness, i.e. the edges to the lesions(s) could just be felt.

Table 3 contains the response rates for this trial.

Table 3

*Percentage of Subjects with Absent or Very Mild Disease According to the Investigator's Global Assessment of Disease Severity at End of Treatment (4 weeks).**

	Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment N = 490	Calcipotriene N = 480	Betamethasone dipropionate N = 476	Vehicle N = 157
Absent or very mild disease	48.0%	16.5%	26.3%	7.6%

*Subjects with mild disease at baseline were required to have "Absent" disease to be considered a success.

In addition to the pivotal trial (N = 490), four randomized, double-blind, vehicle- or active-controlled, parallel-group trials were conducted and provided supportive evidence of efficacy. These studies included a total of 1,058 subjects treated with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment once daily for up to 4 weeks.

16 HOW SUPPLIED

16.1 How Supplied

Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% Ointment is off-white to yellow in color, available in collapsible tubes of:

60 gram (NDC 0781-7165-35)

100 gram (NDC 0781-7165-95)

16.2 Storage

Store calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

16.3 Handling

Keep out of reach of children.

17 INFORMATION FOR PATIENTS

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Inform patients of the following:
- This medication is to be used as directed by the physician.
- It is for external use only.
- Avoid contact with the face or eyes. If this medicine gets on face or in eyes, wash area right away.
- Wash hands after application.
- This medication should not be used for any disorder other than that for which it has been prescribed.
- The treated skin area should not be bandaged or otherwise covered as to be occlusive, unless directed by the physician. Patients should report any signs of adverse reactions to their physician.
- Other products containing calcipotriene or a corticosteroid should not be used with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment without first talking to the physician.
- Instruct patients who use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients who use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.

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Manufactured by
TOLMAR Inc.
Fort Collins, CO 80526 for
Sandoz Inc.
Princeton, NJ 08540

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SPL PATIENT PACKAGE INSERT

Patient Information

Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% Ointment

Read the Patient Information that comes with calcipotriene 0.005% and betamethasone dipropionate

0.064% ointment before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

Important information: Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is for use on the skin only (topical use only). Do not use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the face, under arms or on groin area. **Do not swallow calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.** Another product, Taclonex Scalp[®] Topical Suspension contains the same medicine that is in calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment and is used to treat psoriasis vulgaris on the scalp. If you use both medicines to treat your psoriasis vulgaris, be sure to follow your doctor's directions carefully so that you do not use too much of one or both of these medications.

What is calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment? Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is a prescription medicine that is for use on the skin only (a topical medicine).

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is used to treat psoriasis vulgaris in adults 18 years of age and older.

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is not recommended for use in children. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment has not been studied in patients under the age of 18.

Who should not use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment?

Do not use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment if you:

- **have a calcium metabolism disorder**
- **have one of the following types of psoriasis**
 - erythrodermic psoriasis
 - exfoliative psoriasis
 - pustular psoriasis
- have severe kidney or liver disease
- have thin skin (atrophy) at the site to be treated
- **are allergic to anything in calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.** See the end of this leaflet for a complete list of ingredients.

What should I tell my doctor before using calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment?

Tell your doctor about all of your health conditions, including if you:

- **have a skin infection.** Your skin infection should be treated before starting calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.
- **are getting phototherapy treatments (light therapy) for your psoriasis.**
- **are pregnant or planning to become pregnant.** It is not known if calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment can harm your unborn baby. You and your doctor will have to decide if calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is right for you while pregnant.
- **are breastfeeding.** It is not known if calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment passes into your milk and if it can harm your baby.

Tell your doctor about all the medicines you take, including prescription, and nonprescription medicines, vitamins and herbal supplements.

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment and some other medicines can interact with each other. Especially tell your doctor if you use:

- other corticosteroid medicines

- other medicines for your psoriasis

How should I use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment?

- **Use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment exactly as prescribed by your doctor.**
- Do not use more than the maximum recommended weekly amount of 100 grams of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.
- Apply calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment once a day to the areas of your skin affected by psoriasis. Gently rub calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment into your affected skin areas.
- Only use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment as directed by your doctor. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is recommended for up to 4 weeks of treatment. Do not use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment for more than 4 weeks unless prescribed by your doctor.
- Do not use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the face, under arms or on groin area. If you accidentally get calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment on the face or in the eyes wash the area with water right away.
- If you forget to use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, use it as soon as you remember. Then go on as before.
- Wash your hands well after applying calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.

Using calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment:

- Do not bandage or tightly cover the treated skin area.
- Remove the cap and check that the aluminum seal covers the tube before the first use. To break the seal, turn the cap over and punch through the seal.

What should I avoid while using calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment? Avoid spending a long time in the sunlight. Avoid tanning booths and sunlamps. Use sunscreen if you have to be in the sunlight. Talk to your doctor if you get a sunburn.

What are the possible side effects of calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment?

The most common side effects are:

- itching
- rash

Other less common side effects with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment include:

- redness of the skin
- skin irritation
- skin burning
- inflamed hair pores (folliculitis)
- change of skin color (at the site of application)
- rash with pus-filled papules
- thinning of the skin (atrophy)
- swollen fine blood vessels (this makes your skin appear red at the site of application)

Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment may cause serious side effects. Serious side effects are more likely to happen if you use too much calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, use it for too long, or use it with other topical medicines that contain corticosteroids, calcipotriene, or certain other ingredients. Check with your doctor before

using other topical medicines. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment can pass through your skin. Serious side effects may include:

- **too much calcium in your blood or urine**
- **adrenal gland problems**

Your doctor may do special blood and urine tests to check your calcium levels and adrenal gland function while you are using calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment.

Call your doctor about any side effect that bothers you or that does not go away.

These are not all of the side effects with calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment. Ask your doctor or pharmacist for more information.

How should I store calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment?

- Store calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].
- Make sure the cap on the tube is tightly closed.
- Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment has an expiration date (exp.) marked on the tube. Do not use the ointment after this date.
- **Keep calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment and all medicines out of the reach of children and pets.**

General information about calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment for a condition for which it was not prescribed. Do not give calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment that is written for health professionals.

What are the ingredients in calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment?

Active ingredients: calcipotriene, betamethasone dipropionate

Inactive ingredients: caprylic/capric triglycerides, diazolidinyl urea, dl-alpha tocopherol, white petrolatum.

Call your doctor for medical advice about side effects. You may report side effects to Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Rx only

Taclonex Scalp® is a registered trademark of LEO Pharma A/S Corporation.

Manufactured by

TOLMAR Inc.

Fort Collins, CO 80526 for

Sandoz Inc.

Princeton, NJ 08540

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PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0781-7165-35

**Calcipotriene 0.005% and
Betamethasone Dipropionate 0.064%
Ointment**

FOR TOPICAL USE ONLY. Do not use on your face, underarms or on your groin.

R_x only

NET WT. 60 g

 **SANDOZ**

Each gram contains: 50 mcg of calcipotriene and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of caprylic/capric triglycerides, diazolidinyl urea, dl-alpha tocopherol and white petrolatum.

Usual Dosage: Apply once daily, or as directed by physician. See insert for complete information.

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. Lot no. and expiration date on crimp of tube.

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

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02228 Rev. 0 09/12

NDC 0781-7165-95

**Calcipotriene 0.005% and
Betamethasone Dipropionate 0.064%
Ointment**

FOR TOPICAL USE ONLY. Do not use on your face, underarms or on your groin.

R_x only

NET WT. 100 g

 **SANDOZ**

Each gram contains: 50 mcg of calcipotriene and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of caprylic/capric triglycerides, diazolidinyl urea, dl-alpha tocopherol and white petrolatum.

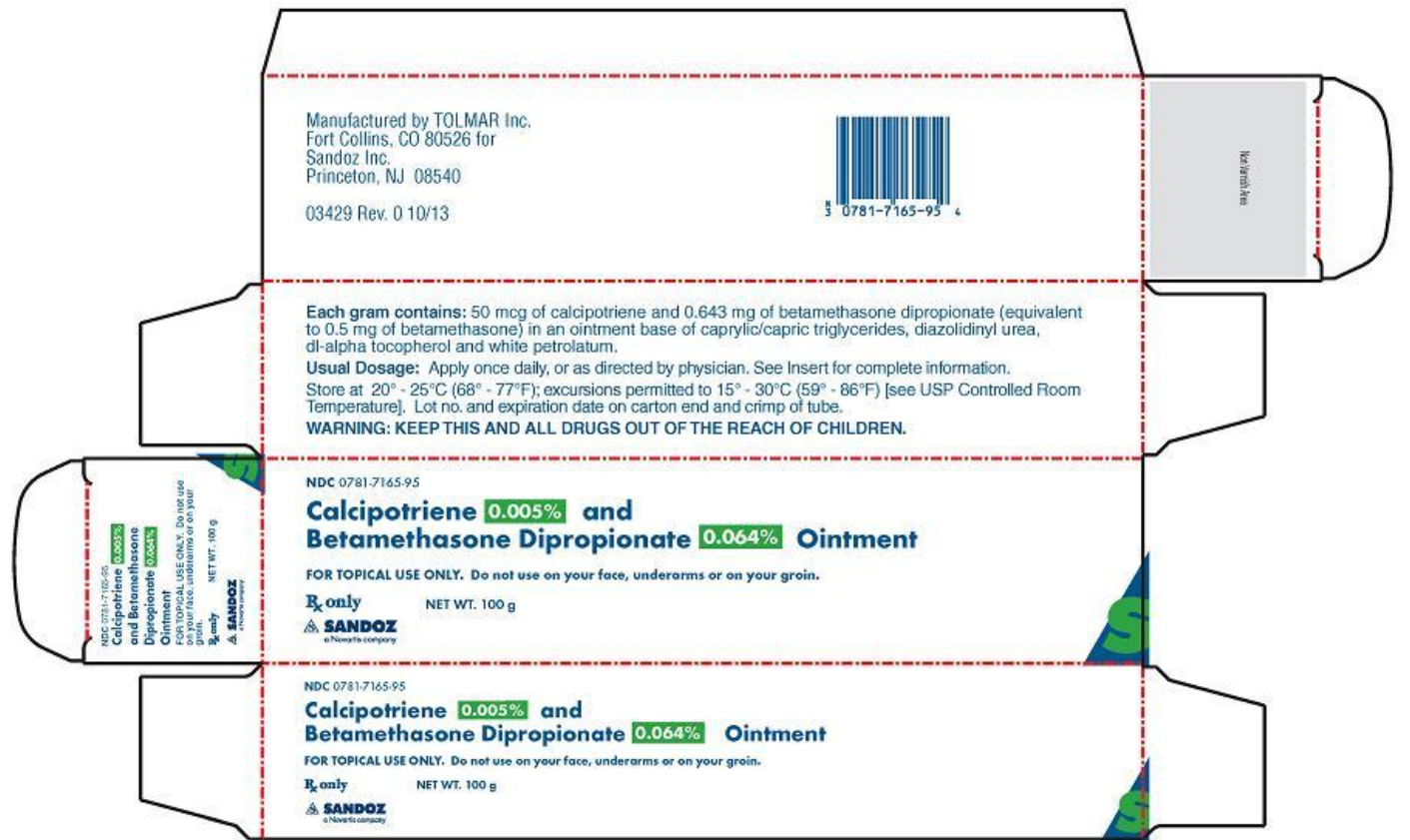
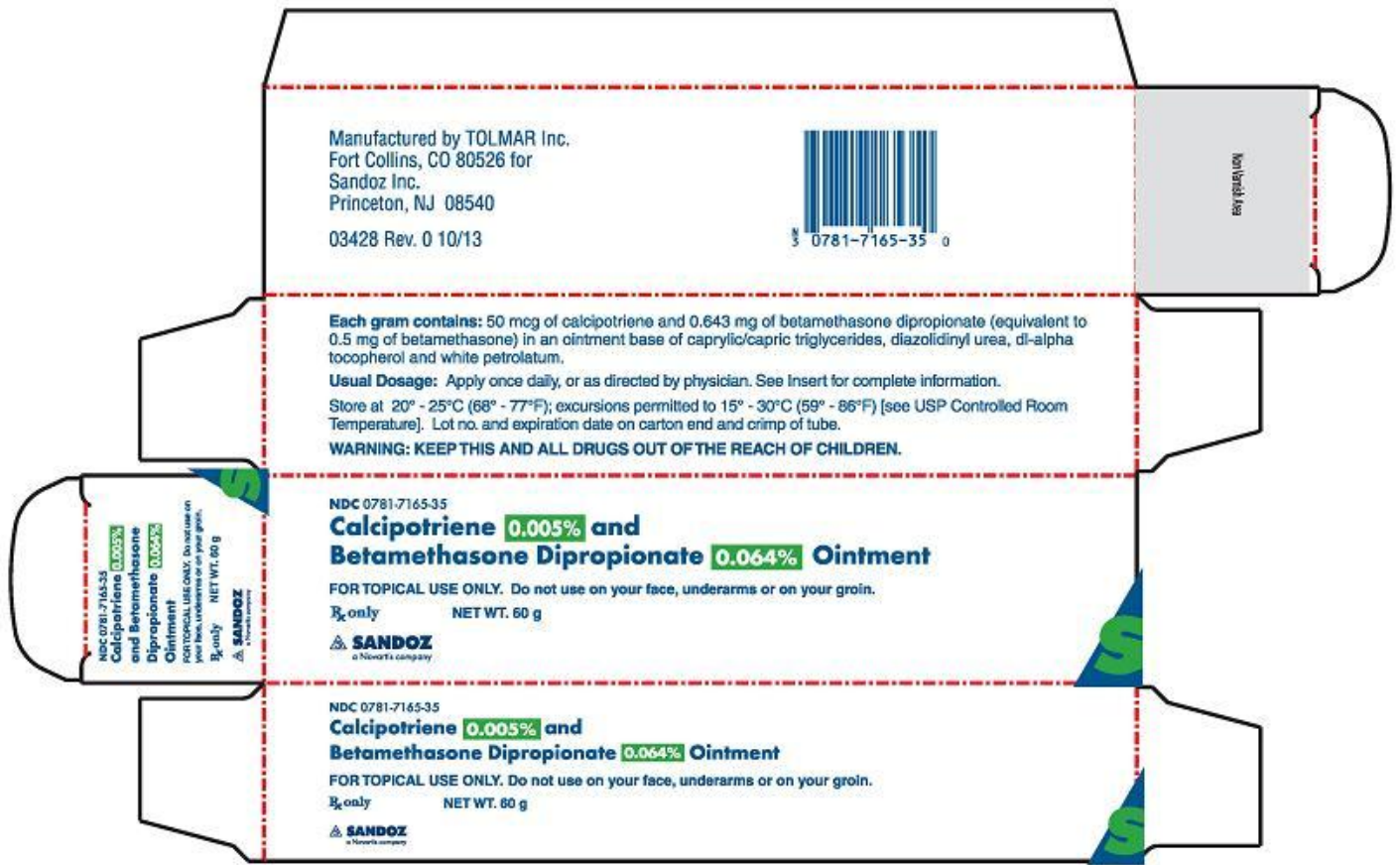
Usual Dosage: Apply once daily, or as directed by physician. See insert for complete information.

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. Lot no. and expiration date on crimp of tube.

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

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02229 Rev. 0 09/12



CALCIPOTRIENE 0.005% AND BETAMETHASONE DIPROPIONATE 0.064%
 calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0781-7165
Route of Administration	TOPICAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CALCIPO TRIENE (CALCIPOTRIENE)	CALCIPOTRIENE	50 ug in 1 g
BETAMETHASONE DIPROPIONATE (BETAMETHASONE)	BETAMETHASONE	0.5 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
MEDIUM-CHAIN TRIGLYCERIDES	
DIAZOLIDINYL UREA	
ALPHA-TOCOPHEROL	
PETROLATUM	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-7165-35	1 in 1 CARTON		
1		60 g in 1 TUBE		
2	NDC:0781-7165-95	1 in 1 CARTON		
2		100 g in 1 TUBE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201615	03/31/2014	

Labeler - Sandoz Inc. (110342024)**Establishment**

Name	Address	ID/FEI	Business Operations
TOLMAR Inc.		791156578	MANUFACTURE(0781-7165), ANALYSIS(0781-7165), LABEL(0781-7165), PACK(0781-7165), API/FDF ANALYTICAL TESTING(0781-7165), FDF MANUFACTURE(0781-7165)

Revised: 3/2014

Sandoz Inc.